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DRUG DELIVERY TO THE BRAIN BY WAY OF NASAL ADMINISTRATION, TWENTY EFFECTIVE DRUGS, THEIR PROPERTIES, AND SCREENING METHOD TO IDENTIFY DRUGS FOR SIMILAR DELIVERY

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ABSTRACT

The blood-brain barrier imposes restrictions on delivery of drugs to the brain. To circumvent these restrictions and to target the brain, investigators have pursued the study and implementation of nasal delivery of various drugs. This study examines the molecular properties of 20 pharmaceuticals that are administered through the nose in order to maximize delivery, achieve higher doses, and/or increase the speed of reaching the brain. The pathologies that can be treated in this manner include: Parkinsons's disease, brain stroke, Alzheimer's disease, depression, epilepsy, migraines, seizures, and sedation (as part of clinical treatment). Specific molecular properties determined and evaluated, will include: mass, Log P, polar surface area, hydrogen bond acceptors, hydrogen bond donors, number of atoms, refractivity, and violations of the Rule of 5. These are properties associated with evaluating drug-likeness (referring to drug absorption or permeation). Summary statistics of the molecular properties for these 20 pharmaceuticals is accomplished, to include mean, minimum, maximum, and 95% confidence interval of properties, which in turn can be utilized to evaluate other drugs for potential nasal administration. Pattern recognition methods such as nearest neighbor cluster analysis, Convex Hull, and box plots, shows interrelationships within their molecular properties of this group of 20 nasal administered drugs. Multiple regression analysis produces a mathematical equation accounting for a high level of variance within this multivariate table of molecular properties and can be applied in the design of similar acting pharmaceuticals. Altogether, this study presents an approach to identify other drugs that can be anticipated to be successful for nasal administration.

KEYWORDS: nasal administration, Parkinson's, Alzheimer's, migraine, depression.

INTRODUCTION

Introduction of medicaments through the nose has been utilized for centuries, and for practical reasons since nasal administration has the following advantages: 1) Avoiding of first-pass metabolism in the liver which results in increased bioavailability, 2) Reduced risk of pain, 3) Effective for drugs requiring low dosage, 4) Efficacy for patients having digestive disorders, 5) Enables rapid administration with rapid drug action, 6) Enables greater patient compliance.[1] In addition, this method allows the by-pass of the blood-brain barrier (BBB) and enable direct administration to the brain.[1] However, the nasal administration is not available to all clinical pharmaceuticals.[2] There is also to be considered the limitation on bio-availability of the drug due to reduced quantity of the nasal administered drug, with metabolism of the drug on the mucosal surface, and potential irreversible damage to the nasal mucosa as additional limitations/problems.[2] Nevertheless, the BBB does impose restrictions on delivery of drugs to the brain and therefore alternate methods of administration remain compelling. For neurodegenerative pathologies which include Alzheimer's disease, Parkinsons's disease, stroke, and brain tumors, there is the necessity of efficient delivery of drugs directly to the central nervous system, which is of great importance.[2]

Generally, it is accepted that the absorption of drugs via nasal administration takes place through a number of pathways.[3] A notable pathway is transfer through an aquatic pathway, also referred to as the paracellular pathway, but is considered to be slow.[3] By the paracellular pathway the absorption of drugs is limited by the molecular weight, in which high molecular weight drugs have significantly lower bioavailability.[3] There is a lipoidal pathway for drugs, but this also affects bioavailability of the drug, which depends on their lipophilicity.[3] Then there is the active transportation of drugs through the cell membranes by opening tight junctions.[3] The nasal cavity has a large quantity of blood vessels that line the mucosa.[3] Generally, the mechanism by which drugs enter the body via the nasal passage include: 1) Transfer by the aquatic pathway or paracellular pathway (slow); 2) Transcellular process (lipoidal pathway); and 3) Active transportation through cell membranes by the opening of tight junctions.[3] However, when directly targeting the brain, the main route is passage of drugs through the olfactory epithelium, followed by movement along the neuron axons to the olfactory bulb.[3] Also, drugs can be absorbed via endocytosis into the neurons, as well as diffuse through the nasal membrane into the cerebrospinal fluid.[3] Drugs can also reach the brain stem and additional portions of the central nervous system (CNS) via travel along the trigeminal nerve.[3]

Types of pathologies that can be treated by use of nasal administration of drugs followed by entrance to the brain include: movement disorders, cerebrovascular diseases, cognitive dysfunction disease, mental illness, neurological diseases (epilepsy), and migraine.[4] Treatment of these disorders is possible due to the direct anatomical pathway from the nasal cavity to the brain[4] This study examines the molecular properties of 20 such used pharmaceuticals.

Statistical analysis reveals commonality among these nasal administered drugs, which are utilized for entry in the CNS. Methodologies utilized in the study to identify other drugs for targeting the brain by nasal administration, will utilize pattern recognition methods such as Convex Hull, Discriminant analysis, principal component analysis (prior to Convex Hull), and summary statistics. Multiple regression analysis produced a formula by which design of similar drugs can be enabled.

MATERIALS AND METHODS

Molecular Properties Determination and Molecular Modeling

The calculation for numerical values of molecular properties such as Log P, polar surface area, molecular weight, number of atoms, refractivity, hydrogen bond donors and hydrogen bond acceptors, and violations of the Rule of 5, for all compounds was determined by Mcule (mcule.com, Palo Alto California USA). For use of Mcule, it is possible to input the SMILES (Simplified Molecular Input Line Entry System) identification of the compound, to procure an extensive list of molecular properties. For imaging of the molecular structures of drugs and determination of various molecular properties, can be accomplished by use of ACD ChemSketch Modeling v. 12.01 (Advanced Chemistry Development, 110 Yonge Street, Toronto Ontario, M5C 1T4 Canada). The environmental software EPI Suite can also be utilized for molecular properties determination (US EPA Estimation Programs Interface v. 1.40, 2012, epa.com).[5]

Pattern Recognition, Statistical Analysis, and Multiple Regression Evaluation

The determination and evaluation of multiple regression analysis, in addition to summary statistics (i.e. 95% confidence interval, median, mean, minimum, maximum, and standard deviation), was accomplished utilizing GraphPad Instat Statistical Analysis Package v. 3.06 2003 (copyright 1992-2003 GraphPad, www. graphpad.com). Pattern recognition analysis that utilized principal component analysis (PCA) followed by Convex Hulls and box plots were accomplished utilizing PAST version 2.15 (copyright Hammer and Harper, 1999-2012).[6]

RESULTS AND DISCUSSION

Nasal administration of suitable pharmaceuticals allows for rapid delivery direct to the brain and without encountering the BBB, which can substantially reduce drug availability.[1] Anatomically, the area of the nose of interest for nasal delivery includes the olfactory epithelium of the upper space, the respiratory epithelium of the lower space, and the second division of the underlying branches for the trigeminal nerve.[1] The precise anatomical location that the drug is administered within the nose can matter significantly.[1] The 20 drugs studied here have a well established success history of clinical nasal administration for the clinical treatment of disorders of the CNS. These 20 drugs have notable commonality of various molecular properties, yet a very diverse assemblage of pathological conditions of the brain for which they are utilized.[1,4] Investigations have shown that nasal administration of drugs for targeting the brain, and with the appropriate drugs, can substantially enhanced emotional conditions and cognitive ability.[4] The 20 drugs presented here have history of successful nasal administration for treatment of CNS disorders.[1,4] The molecular properties for these CNS targeting 20 nasal administrated drugs are shown in Table 1. Previous studies have shown that these molecular properties are effective to evaluate drug-likeness and potential bioavailability, a vital parameter of drug efficacy.[7] Properties shown, such as mass, Log P, number of hydrogen bond donors, and hydrogen bond acceptors, are incorporated into a screening of formulary, referred to as Rule of 5.[7] The Rule of 5 states that a pharmaceutical having the following properties, will have favorable drug-likeness in terms of permeability and oral absorption, if having no more than one violation of the following criteria: 1) Molecular weight less than 500 Daltons; 2) Number of hydrogen bond donors less than or equal to 5; 3) Number of hydrogen bond acceptors less than or equal to 10; 4) A value of Log P less than or equal to 5.[7] In addition, polar surface area is shown to be descriptive of drug-likeness, as is refractivity.[8,9] Polar surface area values of drugs are actually the summation of the surface area of polar atoms (oxygen and nitrogen) along with any hydrogen atoms bonded to them.[8] Whereas, the refractivity is a descriptor that shows relationship of both the volume of the molecule and the molecule's polarizability.[9]

Looking at Table 1, it is immediately noticed that there is a broad variety of central nervous system pathology that can be treated by means of nasal administration of pharmaceuticals. This aspect is encouraging and demonstrates the efficacious potential for nasal administration of drugs. Careful examination of the molecular properties for these 20 successful drugs is warranted in order to determine the range of their numerical values, so that effective screening and recognition of additional drugs for nasal administration can be accomplished.

Table 1: Molecular Properties of 20 Nasal Administered Pharmaceuticals.

Drug (use)	Mass	Log P	Polar Surface Area (A^2)	Hydrogen Bond Acceptors	Hydrogen Bond Donors	Number of Atoms	Refractivity	Violations of Rule of Five
Dexmedetomidine (sedation)	200.3	3.18	28.7	2	1	31	62.8	0
Diazepam (seizures)	284.7	2.65	32.7	3	0	33	88.0	0
Midazolam (seizures)	325.8	3.76	30.2	4	0	36	92.8	0
Sertraline (depression)	306.2	5.57	12.0	1	1	37	86.0	1
Esketamine (depression)	237.7	3.29	29.1	2	1	32	66.0	0
Quercetin (depression)	302.2	1.99	131.4	7	5	32	78.0	0
Perampanel (epilepsy)	349.4	4.44	58.7	4	0	42	105.4	0
Carbamazepine (epilepsy)	236.3	4.15	46.3	3	1	30	76.0	0
Midazolam (epilepsy)	325.8	3.76	30.2	4	0	36	92.8	0
Resveratrol (Alzheimer's)	228.2	2.97	60.7	3	3	29	67.9	0
Benzgalantamine (Alzheimer's)	391.5	3.65	48	5	0	54	113.7	0
Valsartan (brain stroke)	435.5	4.16	112.1	8	2	61	122.9	0
Salvinorin A (brain stroke)	432.5	3.00	109.1	8	0	59	107.4	0
Dihydroergotamine (migraine)	583.7	2.29	118.2	10	3	80	170.0	1
Zavegepant (migraine)	638.8	3.59	120.7	11	9	93	199.7	2
Sumatriptan (migraine)	295.4	2.79	73.6	5	2	41	82.1	0
Zolmitriptan (migraine)	287.4	2.25	57.4	5	2	42	86.2	0
Haloperidol (Parkinson's)	375.9	4.37	40.5	4	1	49	105.5	0
Rotigotine (Parkinson's)	315.5	4.27	51.7	2	1	47	95.2	0
Rasagiline (Parkinson's)	171.2	2.29	12.0	1	1	26	54.5	0

Interestingly, only zavegepant (migraine) has more than one violation of the Rule of 5 (RO5), whereas most other drugs have zero violations (see Table 1, sertraline has one violation and dihydroergotamine has one violation). This outcome indicates all remaining drugs have favorable drug-likeness in permeation and oral availability according to parameters of RO5.[7] Applying box plots and summary statistics, commonalities among this group of pharmaceuticals can be identified and utilized to screen for additional pharmaceuticals for similar clinical use.

Box plots shown in Figure 1, present useful visual interrelationships of the numerical values for these molecular properties, clearly showing the very narrow range of values permissible for Log P, hydrogen bond acceptors, hydrogen bond donors, and Rule of 5. Box plots can be utilized to identify distribution ranges of numerical values, revealing outliers, comparing groups of interest, and visualizing the numerical variations.[10,11] Interestingly, the numerical range of mass is quite broad and has the broadest numerical range of this group of descriptors.

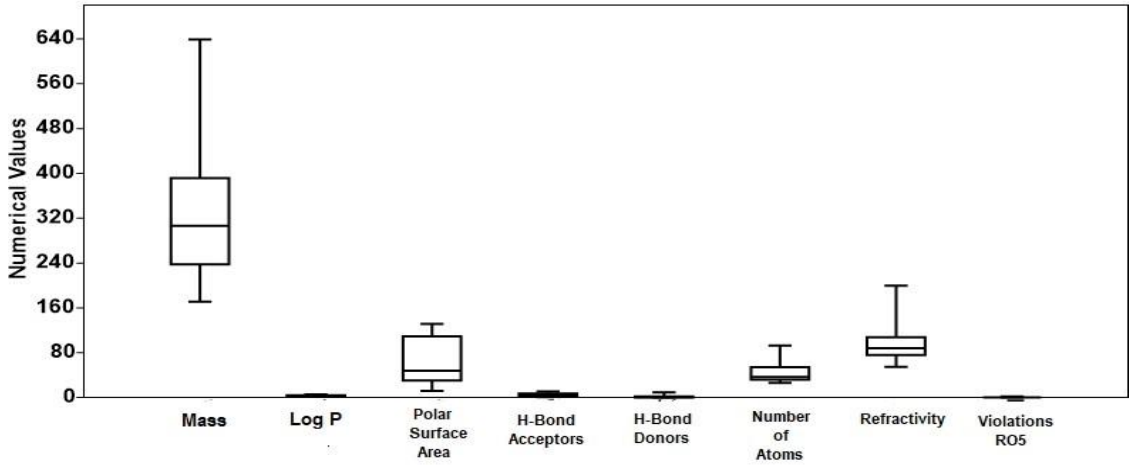

Figure 1: Box plots of molecular properties for 20 pharmaceuticals utilized for nasal administration and clinical treatment of disease (see Table 1).

Summary statistics for these properties are presented in Table 2, these statistics showing a simplification of this data set with mean, median, maximum, minimum, 95% confidence interval of variables, and can be used for comparison of numerical values.[10,11] In addition, Table 2 can be utilized for the selection and elimination of potential drugs for nasal administration. The numerical ranges of these descriptors are easily discerned and can be used to evaluate other drugs that fall into the various classes of relevant pathology (see Table 1, Table 2). Utilizing nasal administration is considered a direct insertion of drugs into the central nervous system (CNS), these are drugs that are generally accepted to be CNS-active drugs and have direct action on the CNS (and by-passing the blood-brain barrier).[12] Examining Table 1 and Table 2, reveals that many of these 20 drugs have molecular properties considered maximal for CNS active drugs.[12] The properties for CNS active drugs include: mass below 400 to 500 Daltons (all of these 20 drugs except valsartan, salvinorin A, dihydroergotamine, zavegepant), less than three hydrogen bond donors (all of these 20 drugs except quercetin, resveratrol, dihydroergotamine, zavegepant), Log P 1.5 to 4 (all of these 20 drugs except sertraline, perampanel, carbamazepine, valsartan, haloperidol, rotigotine), and PSA less than 60 to 90 Angstroms^2 (all drugs of these 20 drugs except quercetin, valsartan, salvinorin A, dihydroergotamine, zavegepant).[7,8,9]

Table 2: Summary Statistics of 20 Nasal Administered Pharmaceuticals.

Parameter	Mass	Log P	Polar Surface Area (A²)	Hydrogen Bond Acceptors	Hydrogen Bond Donors	Number of Atoms	Refractivity	Violations Rule of 5
Mean	336.2	3.42	60.2	5	2	45	97.6	0
Standard Deviation	$1.2x10^2$	0.92	38.0	3	2	18	35.0	1
95% Confidence Interval	281.1-391.3	3.00-3.85	42.4-78.0	3-6	1-3	36-53	81.3-114.0	0-1
Median	310.9	3.44	49.9	4	1	39	90.4	0
Minimum	171.2	1.99	12	1	0	26	54.5	0
Maximum	638.8	5.57	131.4	11	9	93	199.7	2

Multiple Regression Analysis of Properties for 20 Nasal Administered Pharmaceuticals Multiple regression analysis produces very useful denouement from a multivariate set of data. The outcome shows relationships of multiple independent variables (predictors) to merely one dependent variable (outcome).[10,11] Applications of multiple regression analysis accomplishes various purposes, such as prediction (values of the dependent variable), explanation how independent variables interact to affect outcomes, isolation of influence for each independent variable, and assess importance of each independent variable.[10,11] Applying the numerical values of molecular properties presented in Table 1, into multiple regression analysis produced the following regression equation (H-acceptors = Hydrogen bond acceptors, H-donors = Hydrogen bond donors, PSA = Polar surface area, RO5 = Rule of 5).,

Mass = 22.024 + (7.727)(Log P) + (0.2767)(PSA) + (10.796)(H-acceptors) – (9.368)(H-donors) + (0.8964)(Number of atoms) + (1.966)(Refractivity) + (24.972)(RO5)

The value of coefficient of determination or R^2 is 0.9887, indicating that this model accounts for 98.87 percent of the variance in the mass (dependent variable). This outcome indicates that the model is an excellent fit to this set of data (see Table 1).[10,11] The independent variables of refractivity (*P=.003*), and Hydrogen-bond donors (*P=.03*), make the most significant contribution to the model. The F-statistic for this model is 149, which indicates an extremely high ratio (e.g., the variance between the independent variables is 149 times larger than the variance within the independent variables). The value of the F-statistic indicates these independent variables account for a large amount of the variation and the overall model is highly significant.[10,11] Overall, this regression model will be highly useful for determination of properties and identification of additional successful and effective ancillary pharmaceuticals.

Three Drugs Suitable For Nasal Administration

Now, summary statistics and pattern recognition methods will be demonstrated to be useful tools for identifying new nasal administered drugs. Having determined the drug-likeness molecular properties of 20 successful nasal administered drugs, it will be possible to identify other pharmaceuticals having comparable molecular properties to evaluate for nasal administration.

Table 3 shows three such pharmaceuticals along with their identical molecular properties as shown in Table 1. The three drugs and the pathology for which they are applied, are as follows: ergosterol (antifungal), tioconazole (antifungal), and methicillin (antibiotic).

Direct comparison of Table 3 properties to the minimum and maximum values shown in Table 2 for the 20 successful drugs, reveals all properties of these three suitable drugs (ergosterol, tioconazole, and methicillin) fall within the minimum and maximum ranges except for Log P values. The inspection of summary statistics presented in this study, is useful and provides a practical mechanism for identifying potential new nasal administrated pharmaceuticals.

Application of pattern recognition methods enable identification of trends, anomalies, structure, and interrelationhips within a multivariate set of data.[10,11] Nearest-neighbor cluster analysis will provide a visual arrangement of drugs, based on analysis of the multivariate dataset of molecular properties, in a manner in which all drugs having the greatest similarity in molecular properties are nearest and adjacent to each other.[10,11] Drugs that are most similar to each other,.

Table 3: Molecular Properties of Three Drugs Suitable for Nasal Administration.

Drug/use	Mass	Log P	Polar Surface Area (A^2)	H-Bond Acceptors	H-Bond Donors	Number of Atoms	Refractivity	Violations of Rule of 5
Ergosterol (antifungal)	396.65	7.33	20.23	1	1	73	127.47	1
Tioconazole (antifungal)	387.71	5.86	55.29	3	0	36	96.07	1
Methicillin (antibiotic)	380.41	1.28	130.47	8	2	46	98.26	0

are placed in a "cluster" that are apart from the remaining drugs. Figure 2 present nearest- neighbor cluster analysis of all 20 successful drugs (see Table 1) with the three suitable drugs indicated by arrows (21, 22, 23 see Table 3, numbered in descending order).

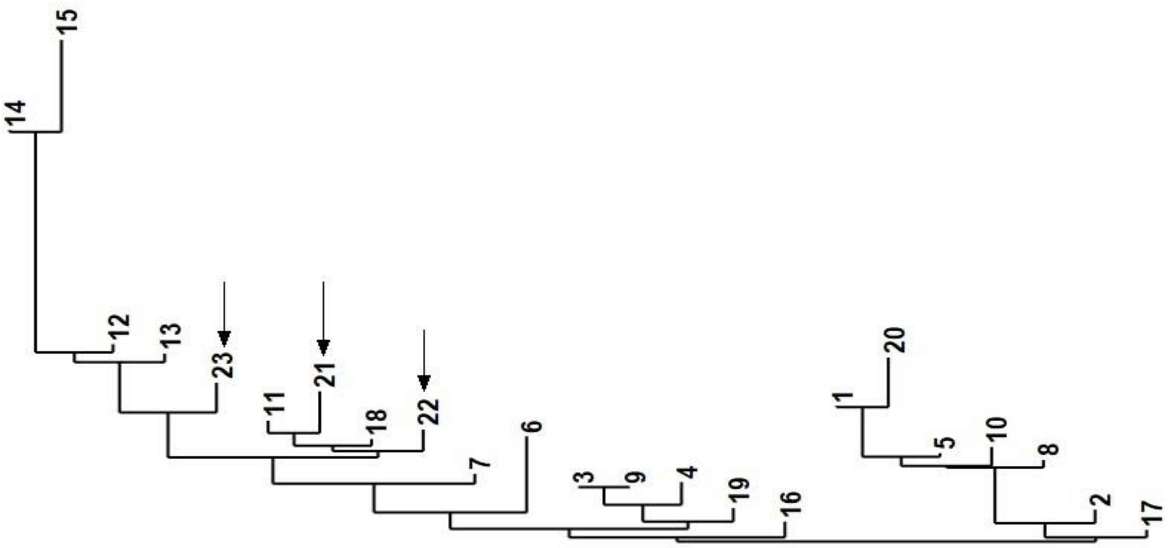

Figure 2: Nearest neighbor cluster analysis (Euclidean distance, single linkage) of 20 nasal administered pharmaceuticals (see Table 1, numbered in descending order) with three additional drugs suitable for nasal administration indicated by arrows as 21, 22, 23 (see Table 3, numbered in descending order). All drugs are positioned adjacent to other drugs that are most similar based on molecular properties. Drug 21 (ergosterol) and drug 22 (tioconazole) are most similar to pharmaceuticals 18 (haloperidol) and 11 (benzgalantamine) based on molecular properties. Drug 23 (methicillin) is closest in similarity to pharmeceutical 12 (valsartan) and 13 (salvinorin A) based on molecular properties.

The outcome presented in Figure 2, indicates visually that the three drugs ergosterol, tioconazole, and methicillin are determined to be highly similar to members of Table 1 (20 successful nasal administered drugs), based on molecular properties, and thereby have excellent potential as nasal administered pharmaceuticals. Specifically, ergosterol (21, see Figure 2) and tioconazole (22, see Figure 2) are most similar to and grouped with benzgalantamine (11, see Table 1) and haloperidol (18, see Table 1). In addition, methicillin (23, see Figure 2) is highly similar to valsartan (12, see Table 1), salvinorin A (13, see Table 1), dihydroergotamine (14, see Table 1), and zavegepant (15, see Table 1). Highly sensitive cluster analysis indicates high similarity to members of the 20 successful nasal administered pharmaceuticals.

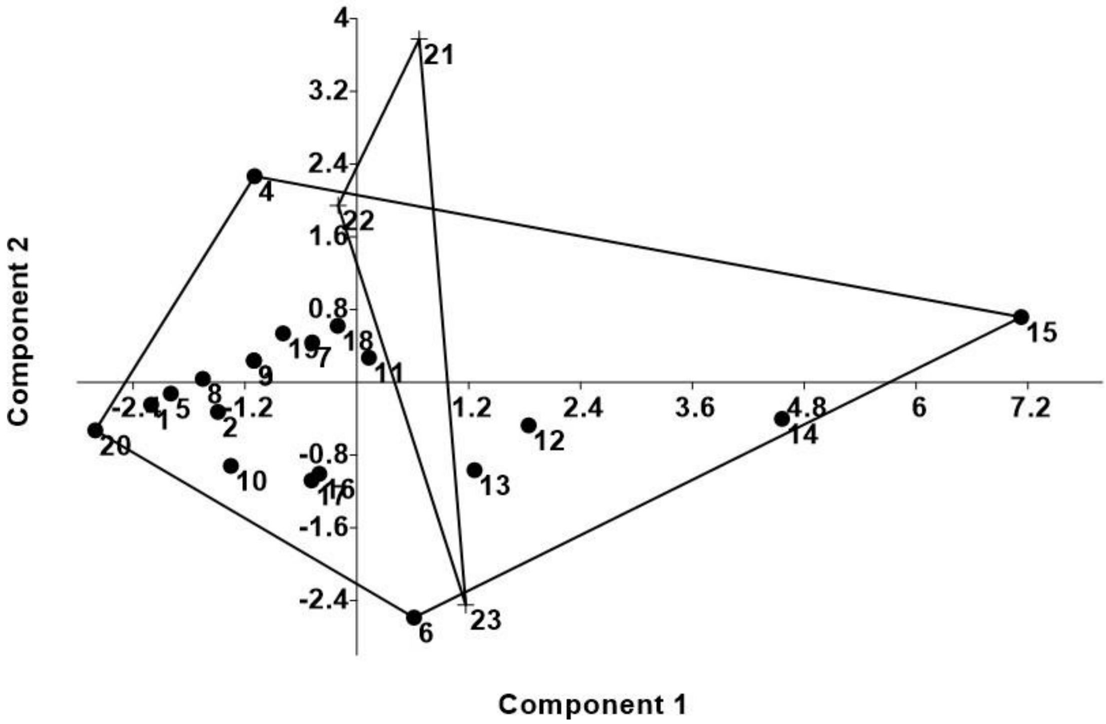

Figure 3: Overlapping Convex Hull for 20 nasal administered pharmaceuticals (see Table 1, numbered in descending order) and three suitable drugs for nasal administration (see Table 3, numbered in descending

order), drug 21 (ergosterol), drug 22 (tioconazole), and drug 23 (methicillin). Overlap of Convex Hull indicates that all drugs analyzed are undifferentiated and comparable based on molecular properties. Therefore, ergosterol, tioconazole, and methicillin are anticipated to be efficient and clinically effective for nasal administration. Convex Hull analysis was accomplished following principle components analysis.

Convex Hull analysis is a pattern recognition method applied in this study to identify drugs of the same category (i.e., have the highest similarity) based on their numerical molecular properties. Convex Hull will also identify outliers, calculate group boundaries, evaluate heterogeneity, and define subjects within a one-class classification.[13,14] Clearly shown in Figure 3 are the overlap of Convex Hull for drugs ergosterol, tioconazole, and methicillin (21 to 23, see Table 3), with the Convex Hull of all 20 successful nasal administered drugs (1 to 20, see Table 1). To summarize, ergosterol, tioconzzole, and methicillin are determined and expected to be effective and successful nasal administered pharmaceuticals.

Three Drugs Not Suitable for Nasal Administration

Having determined the drug-likeness molecular properties of 20 successful nasal administered drugs, it will be possible to recognize other pharmaceuticals, by their calculated molecular properties, that are determined not to function as effective efficacious nasal administered medicaments. Table 4 shows three such pharmaceuticals along with the identical properties as shown in Table 1. The three drugs and the pathology in which they are applied, are as follows: rifampicin (antibiotic), colistin (antibiotic), and vancomycin (antibiotic).

Table 4: Molecular Properties of Three Drugs Not Suitable for Nasal Administration.

Drug (use)	Mass	Log P	Polar Surface Area (A^2)	Hydrogen Bond Acceptors	Hydrogen Bond Donors	Number of Atoms	Refractivity	Violations of the Rule of 5
Rifampicin (antibiotic)	822.9	4.35	220.2	16	6	117	234.2	3
Colistin (antibiotic)	1155.4	1.54	490.7	29	18	179	326.2	3
Vancomycin (antibiotic)	1449.2	3.93	530.5	33	19	176	368.3	3

Direct comparison of Table 4 molecular properties to the minimum and maximum values shown in Table 2 for the 20 nasal administered drugs, reveals mass, polar surface area, H-bond acceptors, H-bond donors (except for rifampicin), number of atoms, refractivity, and violations of RO5, are substantially different and out of range in comparison. Again, inspection of summary statistics is useful and provides a practical mechanism for recognizing drugs not suitable and not predicted to be effective or efficacious for nasal administration. Application of pattern recognition methods, as stated before, are utilized across many diverse disciplines (e.g.,. machine learning, computer computations, medicine, and engineering) enable identification of trends, anomalies, structure, and underlying interrelationhips within a multivariate collection of data.[10,11] Nearest-neighbor cluster analysis of rifampicin, colistin, and vancomycin descriptors' (see Table 4), with those of Table 1 (20 nasal administered drugs) will provide a visual arrangement of drugs, based on analysis of the molecular properties, showing clusters of the most similar drugs in closest proximity and separation from not similar drugs.[21,22,23]

Figure 4 presents the nearest-neighbor clustering outcome, with rifampicin[21], colistin[22], and vancomycin[23], clearly well separated and distinct from all 20 nasal administered drugs. Note that all 20 nasal administered drugs are in the lowest portion of the dendogram and thereby are the greatest similarity, whereas 21 (rifampicin), 22 (colistin), and 23 (vancomycin) have a long branch connecting this cluster and are considerably higher up in the dendogram, clearly indicating no similarity to the nasal administered drugs.

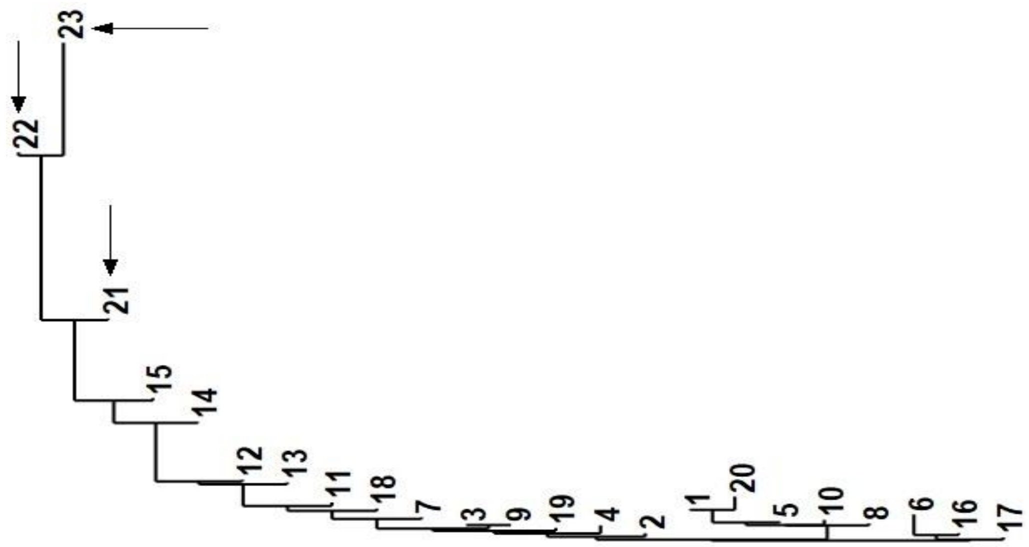

Figure 4: Neighbor joining cluster analysis (Euclidean distance, single linkage) of 20 drugs utilized for nasal administration (Drugs 1 to 20, see Table 1 in descending order) and three drugs not suitable for nasal administration (Drugs 21, 22, 23, see Table 4 in descending order). The three drugs not suitable for nasal administration 21 (rifampicin), 22 (colistin), and 23 (vancomycin) are indicated by arrows, are distinct and are clustered together, but well separated from 20 successful nasal administered drugs.

Convex Hull analysis is a very effective pattern recognition method to identify drugs of the same category (i.e., highest similarity) based on numerical molecular properties, and can identify outliers, calculate group boundaries, evaluate heterogeneity, and define one-class classification[13,14] Clearly shown in Figure 5 are the non-overlap of Convex Hull for drugs rifampin (21, see Table 4), colistin (22, see Table 4), and vancomycin (23, see Table 4), with Convex Hull of all 20 successful nasal administered drugs (1 to 20 in descending order, see Table 1). In summary, rifampicin, colistin, and vancomycin are determined not be efficacious and not successful for nasal administration in the clinical treatment of central nervous system pathology.

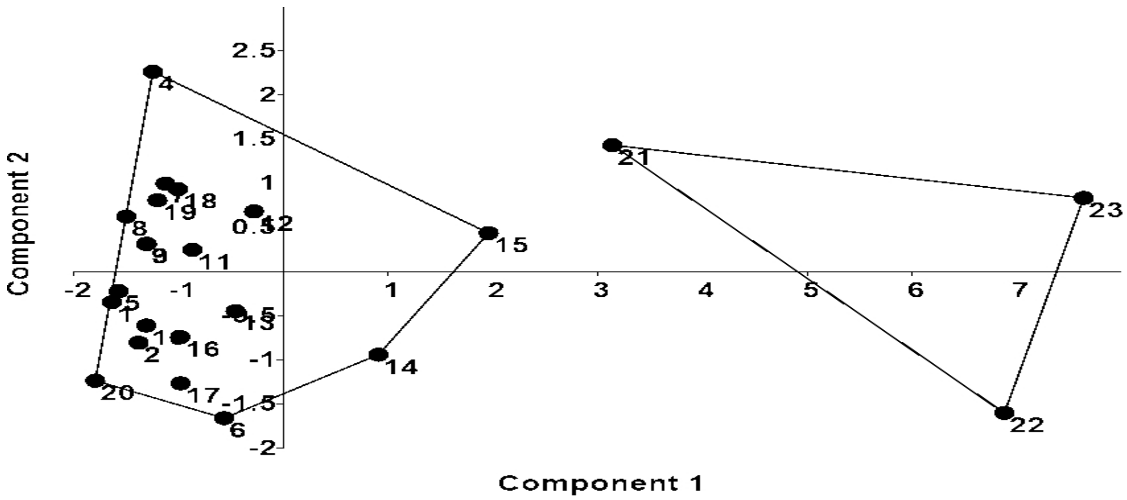

Figure 5: Not overlapping Convex Hull for 20 nasal administered pharmaceuticals (see Table 1, numbered in descending order) and three drugs not suitable for nasal administration (see Table 4, numbered in descending order), which are drug 21 (rifampicin), drug 22 (colistin), and drug 23 (vancomycin). Convex Hull analysis indicates rifampicin, colistin, and vancomycin are not anticipated to be efficient and clinically effective for nasal administration. Convex Hull analysis follows principle component analysis in PAST (see Materials and Methods).

A Discriminant Analysis completed inclusive of all molecular properties of the 20 successful nasal administrated drugs (see Table 1) with the three not suitable drugs (see Table 4), did clearly distinguished and differentiated the 20 successful drugs from the three not suitable drugs (rifampicin, colistin, vancomycin) into two separate groups. The 20 utilized successful drugs placed in group 1, but the three not suitable drugs were identified into a group 2. This finding is further evidence that the molecular properties of the 20 successful nasal administered drugs can be utilized to identify, screen out, and discard any other drug not having favorable molecular properties for nasal administration.

CONCLUSIONS

This study has examined 20 different drugs that are nasal administered for a variety of CNS pathologies that include: Parkinson's, Alzheimer's, cancer, migraine, stroke, depression, seizure, and sedation. After determination of molecular properties, a process important for evaluating drug-likeness, it is found that various commonalities exist among these 20 drugs. Paramount is that all 20 drugs pass the Rule of 5, meaning that these 20 drugs will have favorable permeation, favorable drug absorption, have favorable oral activity, and highly likely to survive clinical testing. Statistical analysis determined the 95% confidence interval, maximum, minimum, and mean for their molecular properties. From this study, the drugs ergosterol (antifungal), tioconazole (antifungal), and methicillin (antibiotic) are identified to be suitable for nasal administration and anticipated to be efficacious. All three of these drugs furthermore pass the Rule of 5 criteria (confirming favorable drug-likeness and bioavailability), have overlapping Convex Hull with the 20 nasal drugs, which indicates congruent similarity of these drug-likeness properties. In addition, their molecular properties fall into acceptable ranges of the maximum, minimum, and 95% confidence range of the 20 effective nasal drugs. However, rifampicin (antibiotic), colistin (antibiotic), and vancomycin (antibiotic) are not suitable for nasal administration, having molecular properties substantially out of bounds of 95% confidence interval of the 20 effective nasal drugs. The Convex Hull analysis for these three antibiotics resulted in well separated hull (not overlapping), from that of the 20 successful nasal administered drugs. In addition, the antibiotics rifampicin, colistin, and vancomycin are distinct and separate from the 20 effective nasal drugs following Discriminant Analysis, in which all 20 nasal drugs fall within a distinct separate grouping from rifampicin, colistin, and vancomycin.

Therefore, statistical analysis with pattern recognition methods have identified two antifungal and one antibiotic that are expected to be effective as nasal administered drugs and having efficacious activity. The antibiotics rifampicin, colistin, and vancomycin are recognized as not suitable for nasal administration, due to adverse molecular properties. This study demonstrating that the use of statistical analysis and pattern recognition methods can be utilized to screen out unsuitable pharmaceuticals for nasal administration.

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REFERENCES

1. Shrewsbury SB. (The pharmacokinetics of drug delivered to the upper nasal space). Pharmaceutical Medicine, 2023; 37: 451-461.
2. Tai J, Han M, Lee D, Park L-H, Lee SH, Kim TH. (Different methods and formulations of drugs and vaccines for nasal administration). Pharmaceutics, 2022; 14: 1073-8.
3. Choudante S, Deshmukh P, Kadam V, Tare H. (Kinetics aspects in design and release of nasal drug delivery systems). International Journal of Drug Delivery Technology, 2024; 14(2): 1191-7.
4. Huang Q, Chen X, Yu S, Gong G, Shu H. (Research progress in brain-targeted nasal drug delivery). Front Aging Neurosci, 2024; 15: 1-12.
5. US EPA. 2012. EPI Suite (Estimation Programs Interface Suite for Microsoft Windows), v. 1.40. United States Environmental Protection Agency, Washington, DC, USA. Web site of US EPA GOV.
6. Hammer O, Harper DAT, Ryan PD. (PAST. Paleontological statistics software package for education and data analysis). Paleontologia Electronica, 2001; 4(1): 1-9.
7. Lipinski CA, Lombardo F, Dominy BW. Feeney PJ. (Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings). Advanced Drug Delivery Reviews, 1997; 46(1-3): 3-26.
8. Prasanna S, Doerksen RJ. (Topological polar surface area: a useful descriptor in 2D-QSAR). Curr Med Chem, 2009; 16(1): 21-41.
9. Padron JA, Carrasco R, Pellon RF. (Molecular descriptor based on a molar refractivity partition using Randic-type graph-theoretical invariant). J Pharm Pharmaceut Sci, 2002; 5(3): 258-266.
10. Davis JC. Statistics and Data Analysis in Geology. New York; John Wiley & Sons, 1986.
11. Freedman DA. Statistical Models: Theory and Practice. New York; Cambridge University Press, 2009.
12. Clark DE. (Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena. 2. Prediction of blood-brain barrier penetration). Journal of Pharmaceutical Sciences, 1999; 88(8): 815-821.
13. Andrew AM. (Another efficient algorithm for convex Hulls in two dimensions). Information Processing Letters, 1979; 9(3): 216-219.
14. Avis D, Brenner D, Seidel R. (How good are convex hull algorithms). Computational Geometry, 1997; 7(5-6): 265-301.