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Enhance The Brain Concentration And Antiepileptic Effect Of Drug Lamotrigine By Encapsulating Inside The Chitosan Coated Nanoliposomes For Intranasal Drug Delivery System

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Abstract

Most potentially active therapeutic chemicals are unable to reach the brain from the systemic circulation due to the blood brain barrier's (BBB) restricted medication entry. Lamotrigine, an AED that may operate as either an enzyme inducer or an enzyme inhibitor, is routinely used in conjunction with other AEDs, and the goal of this study is to evaluate the magnitude of the impact size of concurrent antiepileptic medication on lamotrigine concentrations. A total of 304 epilepsy patients ranging in age from 18 to 70 were randomly assigned to receive either lamotrigine alone or lamotrigine in combination with either an enzyme inducer, an enzyme inhibitor, or both. Lamotrigine's serum concentrations were determined after single-drug, double-drug, and triple-drug dosing with valproate, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and topiramate. Higher amounts of valproate led to greater inhibition and higher lamotrigine concentrations. These results may have therapeutic implications for the best dosage of AEDs to use in patient care.

Keywords: liposomes; intranasal; lamotrine; brain delivery; antiepileptic effect

INTRODUCTION

Encapsulating the medication lamotrigine within chitosan-coated nanoliposomes for intranasal drug delivery has been shown to increase both its brain concentration and antiepileptic efficacy. More than two thousand years ago, Hippocrates hypothesized that a malfunctioning brain was to blame for the convulsions. Hughling Jackson, who in 1875 provided the first contemporary definition of epilepsy, observed that a seizure results from disrupted brain electrical, which may affect awareness, sensation, and behavior. The advent of EEG technology in the 1920s allowed researchers to establish causal links between abnormal brain activity and psychiatric conditions. New and better therapy options are available now as a consequence of developments in medical imaging and genetics. New antiepileptic medications and enhanced versions of existing treatments have been approved for the treatment of epilepsy in the past two decades. The drugs for the treatment of epilepsy have been identified using a number of in vivo and in vitro models. There has been little progress in understanding the cellular basis of epilepsy, and around 30% of epileptic patients are pharmacoresistant; seizures and adverse drug reactions continue to be the predominant causes of morbidity and mortality in this patient group.

To put it simply, lamotrigine is an AED of the second generation. During testing and before to authorisation for sale, its potential for metabolic interactions was identified. So, it was suggested to significantly reduce the dosage. Liver or kidney function, as well as age, play major roles in lamotrigine elimination. Dosage changes may be necessary if lamotrigine is used in conjunction with other antiepileptic drugs (AEDs) that induce enzymes, such as carbamazepine, phenobarbital, phenytoin, and primidone. Lamotrigine metabolism may also be induced by oxcarbazepine and topiramate. Concentrations of lamotrigine might rise by as much as 200% if you take valproate, a potent inhibitor of lamotrigine metabolism. The pharmacokinetic interactions between lamotrigine and valproate have been categorized as level 2 by Johannessen et al. based on the degree of changes in serum

concentration. This means that caution should be exercised and dose adjustments may be necessary if the combination cannot be avoided. UGT1A4 is responsible for the majority of the metabolism of lamotrigine, whereas UGT2B7 is responsible for the majority of the glucuronidation of valproate. UGTs may be inhibited or induced, and their pharmacogenetic susceptibility to variation in drug metabolism has been studied extensively.

Therapeutic drug monitoring is required for lamotrigine because of its large pharmacokinetic variability. Lamotrigine concentrations within the reference range have not been shown to be therapeutically optimum or efficacious, despite the range's apparent breadth. The optimal therapeutic concentration has to be determined for each individual patient. The goal of this study was to determine how various AEDs affected lamotrigine levels in individuals with focal and generalized seizures. This method may aid doctors in estimating the link between antiepileptic medication interactions and illness control, as measured by a decline in the frequency of seizures.

LITERATURE REVIEW

Asha Paul, K.M. Fathima and Sreeja C. Nair (2017), In order to avoid the side effects associated with systemic administration and the drug's first-pass metabolism, For the treatment of epilepsy, we created a novel intranasal mucoadhesive formulation of lamotrigine (LTG) packed insitu gel. The formulations tested met or exceeded the criteria set by the different assessment studies. No mucosal irritation is to be anticipated since the pH of the formulation is within the permitted range of 5.8.001 to 6.8.005. Maximum medication release from the improved G5 formulation of a mucoadhesive insitu gel occurred 20 minutes after incubation at 37 degrees Celsius in an in vitro drug release assay. Exvivo permeation trials have been calculated for both the G5 optimized formulation and the control formulation. Studies of G5 insitu formulation's permeability to the bloodstream in vitro found that it released its drug slowly and steadily over a 12-hour period, with significantly higher permeability through the nasal mucosa compared to the control group (P 0.05). Nasal delivery of the G5 formulation caused no irritation, as shown by histopathological examinations. According to the results of the stability tests, gels may be stored in the refrigerator for up to 45 days at 4°C. For the treatment of acute epileptic disorder.

According to Serralheiro A, Alves G, Fortuna A, Falco A. (2015), One of the main reasons anticonvulsant medicine fails is pharmacoresistance; this calls for the development of novel and more effective treatment strategies. Due to its anatomical proximity to the brain, the nasal cavity has been investigated as a potential route for the preferred delivery of medicines. The current research aimed to evaluate the pharmacokinetics of lamotrigine in mice when given through the intranasal route and to look into the possibility of direct transport of the medication from the nose to the brain.Therefore, intranasal medication administration seems to be a workable and helpful way for the long-term management of epilepsy, providing a potentially useful alternative strategy for the management of pharmacoresistance.

Praveen A, Muhammed Aqil, Syed S. Imam, Ahmad F.J. Ahad, and Thavarajah "T. (2019), The goal of this research was to create LTG-NLs to use in the treatment of seizures. In-vitro release, stability, confocal laser scanning microscopy (CLSM), and nasotoxicity tests were further characterizations of the enhanced LTGNLopt. Nano-sized LTGNLopt was shown to have excellent encapsulation and drug release. Studies using confocal laser imaging and ex vivo permeation demonstrated the increased permeation over the goat nasal mucosa. According to the results, an efficient lipid carrier system for intranasal administration may be achieved by adjusting the independent factors utilized to improve the NLs.

Jayshree B Taksande, et al. (2017), In this investigation, As an antiepileptic, we developed and studied trimethyl chitosan (TMC) mucoadhesive microspheres loaded with Lamotrigine for intranasal administration. To begin, reductive methylation of chitosan was used to create TMC, which was then analyzed by FTIR, DSC, and XRD. Studies on excised sheep nasal mucosa and zeta potential, drug entrapment efficiency, thermal behavior, in vitro

drug release, mucoadhesiveness, biocompatibility, and scanning electron microscopy were conducted on TMC microspheres loaded with lamotrigine. At 29.8 mV zeta potential and PDI of 0.256, the microspheres were found to be smooth and spherical in form, making them ideal for nasal administration. In excised sheep nasal mucosa, the prepared microspheres demonstrated a high encapsulation efficiency of up to 92.340.73%, a robust bioadhesion potential, and a complete lack of morphological toxicity. In batches TL-8 and TL-9 of TMC microspheres, lamotrigine permeation was 88.80% and 83.24%, respectively. Furthermore, there are potential benefits over traditional dose forms when TMC mucoadhesive microspheres are loaded with lamotrigine.

Dmitry Kuznetsov, Mohd Ismail Haron, Renad Alyautdin, Igor Khalin, and Muhammad Huzaimi Haron (2014), The complex structure of the endothelium lining the blood vessels of the brain and the various specialized transport systems expressed on their surface are what give the BBB its protective qualities. Damage to the EC, which is responsible for maintaining the BBB's tight regulation, allows chemicals that are harmless to peripheral tissues but harmful to neurons to enter the CNS more easily (CNS). Hence, neurological illnesses, such as degenerative diseases, may arise at any age. Despite its importance in controlling the metabolic milieu necessary to preserve neuronal integrity, the BBB restricts medication delivery to the central nervous system (CNS). This complicates efforts to protect neurons from neurotoxins while delivering therapeutic medications across the BBB. Drugs may be transported through the ECs in a number of different ways, such as by connecting them to one of the preexisting transport networks or by navigating occludins and claudins at the tight junctions. In any case, only the desired medicine should be able to get through the gate. Many drug-delivery techniques, including alterations to the medicines' innate pumping-out system and the use of nanocarriers and liposomes, have been tried but all have their drawbacks. This paper covers the BBB's functional morphology and the obstacles faced by drug-delivery systems, going into detail about the possible targets, processes, and formulations that may be used to enhance drug administration to the CNS.

METHODS

Patients in this retrospective analysis ranged in age from 18 to 70; all had been diagnosed with epilepsy and treated at the Referral Centre for Epilepsy at University Medical Center Zagreb for either focal or generalized seizures (Figure 1). Standard biochemical measures such as urea, creatinine, and hepatic enzymes were used to rule out patients with impaired hepatic and renal function (Table 1). Medical records from 2009-2013 were gathered from the Neurology and Laboratory Diagnostics departments of the University Hospital Center in Zagreb.

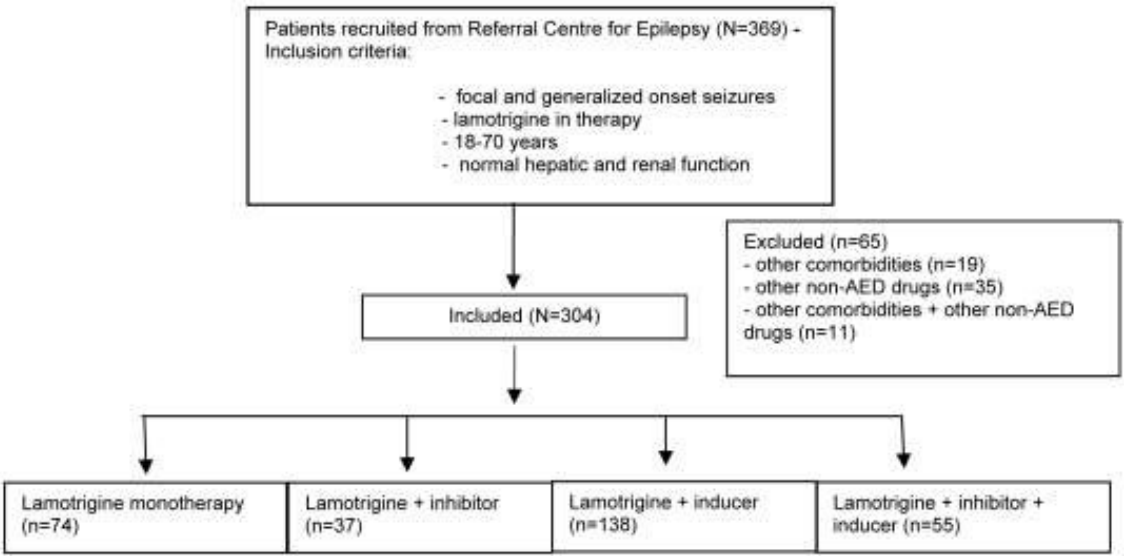

Figure 1. Flowchart of lamotrigine-treated patients with epilepsy

Table 1. Clinical and demographic data on 304 lamotriginetreated patients (126 men)

Parameter	Value (mean±SD)
Age (years)	37 ± 14
Height (cm)	171 ± 9
Body weight (kg)	73 ± 18
Urea (mmol/L)	4.4 ± 1.4
Creatinine (µmol/L)	83.0 ± 17.4
ALT (U/L)	18.9 ± 15.1
GGT (U/L)	58.9 ± 49.9

74 patients had lamotrigine 50–300 mg/day as monotherapy, while 92 patients received it in combination with valproate 600–1500 mg/day, carbamazepine 600–1600 mg/day, oxcarbazepine 600–1800 mg/day, phenobarbital 100–600 mg/day, phenytoin 200–300 mg/day, or topiramate 50–250 mg/day. Vigabatrin, gabapentin, and levetiracetam were also used in the treatment of some of the patients. Patients were grouped into those who were taking lamotrigine alone, those who were using lamotrigine in conjunction with a metabolic inhibitor, those who were taking lamotrigine in conjunction with metabolic inducers, and those who were taking lamotrigine in conjunction with both an inducing agent and an inhibitor.

Therapeutic drug monitoring

Serum concentrations of antiepileptic medications are regularly tested in all patients at the Regional Centre for Epilepsy. This means that all research participants had access to all study-required measures. When at least 21 days of treatment had passed since the drug's content in the blood had settled to a stable level, a single blood sample was taken from each patient. Morning blood samples were taken 12 hours after the evening dosage and 4 hours before the next dose was administered (trough value). High performance liquid chromatography with a fluorescence detector was used to measure the amounts of derivatized vigabatrin and gabapentin. Immunoassay using a Dimension Expand analyzer measured phenobarbital and valproate levels in the blood (Siemens, Erlangen, Germany). Chromsystems (Munich, Germany) supplied the calibrators and controls for the HPLC analysis, while Innofluor and Siemens supplied the reagents for the immunoassay. All of the analytes were put through the ringer at the Reference Institute for Bioanalytical Chemistry and the United Kingdom's National External Quality Assessment Service.

Statistical analysis

Presentation of demographic and clinical data was accomplished via the use of descriptive statistics. The D'Agostino-Pearson test was used to verify the normality of the data, we compared the trough and dose-corrected lamotrigine levels in each treatment group. Kruskal-Wallis tests were used to assess statistical significance between groups since lamotrigine concentration was not regularly distributed in the research population. Spearman's coefficient of rank correlation was used to analyze the relationship between the parameters, and the results were shown as rho values with 95% CIs and P values. The significance threshold was determined to be P0.05. MedCalc version 17.2 was used for all statistical calculations.

RESULTS

Although the median trough concentrations of lamotrigine were all within the standard range (8), those of the majority of other AEDs were much lower (Table 2). After adjusting for dosage, lamotrigine levels in valproate-treated patients remained significantly higher than in any other group (Table 2). The concentration of amotrigine

was lowest in patients receiving lamotrigine alone.

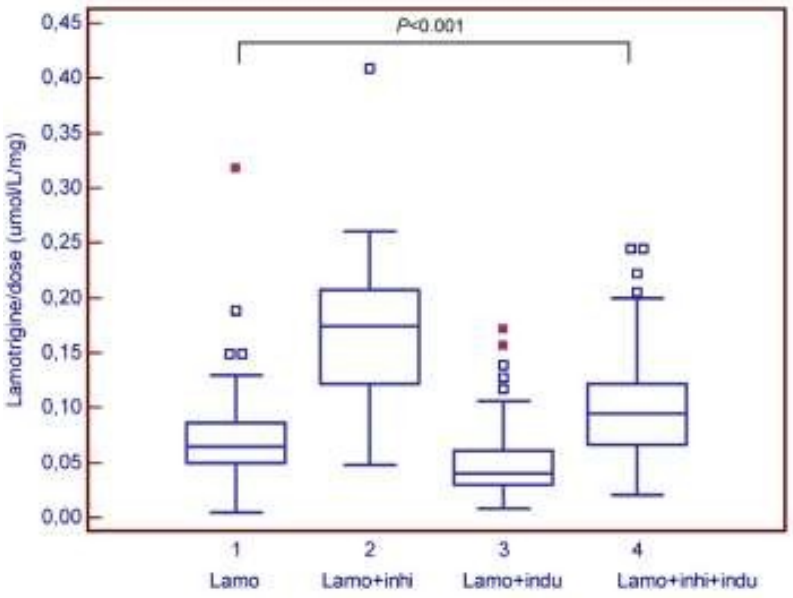

Figure 2. Lamotrigine concentrations adjusted for concurrent antiepileptic medications that suppress or produce seizures.

Table 2. Serum trough- (C) and dose-corrected (C/D) antiepileptic drug (AED) concentrations in lamotrigine-treated patients with epilepsy*

			AED concentrations (median, 5th-95th percentile)	
Therapy	No. of patients	f	C (µmol/L)	C/D (µmol/L/mg)
Lamotrigine	304	3.90	8.6 (2.3-38.9)	0.062 (0.022-0.202)
monotherapy	74		6.4 (1.6-23.5)	0.065 (0.024-0.145)
+ inhibitor	37		25.9 (5.3-50.8)	0.174 (0.059-0.261)
+ inducer	138		6.5 (2.0-21.7)	0.040 (0.017-0.098)
+ inhibitor and inducer	55		15.8 (3.0-57.3)	0.094 (0.044-0.218)
politherapy				
+ valproate	92	6.93	339.7 (128.9-652.9)	0.342 (0.154-0.603)
+ phenobarbital	78	4.31	69.4 (14.1-168.6)	0.246 (0.033-0.673)
+ carbamazepine	110	4.23	32.7 (18.4-53.1)	0.032 (0.018-0.073)
+ MHD	47	3.96	58.0 (22.6-97.7)	0.046 (0.018-0.111)

In patients using both lamotrigine and valproate, we looked at their association, and in those not taking both medicines together, we looked at lamotrigine's correlation with carbamazepine, MHD, and phenobarbital.

Lamotrigine and valproate trough concentrations were positively correlated in a linear fashion, and this relationship strengthened after adjustment for dosage (Table 3). Lamotrigine's trough concentrations correlated poorly with MHD and phenobarbital's, although carbamazepine's correlated positively with MHD upon dosage adjustment. Patients taking lamotrigine in combination with inducers or both inhibitors and inducers in addition to phenytoin were too few for statistical analysis.

Table 3. Correlation of antiepileptic drug (AED) therapy

AED	No. of patients	Lamotrigine (µmol/L)		Lamotrigine/dose (µmol/L/mg)	
		rho (95% CI)*	P	rho (95% CI)*	P
Valproate	87	0.480 (0.298-0.628)	<0.001	0.561 (0.383-0.699)	<0.001
Carbamazepine	85	0.367 (0.166-0.538)	<0.001	0.439 (0.235-0.594)	<0.001
Phenobarbital	56	0.229 (0.036-0.464)	0.09	0.051 (-0.247-0.304)	0.83
MHD	33	0.228 (-0.125-0.530)	0.20	0.675 (0.415-0.833)	<0.001

Initiating therapy at a lower dose resulted in higher lamotrigine blood concentrations than when lamotrigine was used alone or in combination with other AEDs. Due to dose-dependent adverse effects, this finding has clinical relevance. We found that lamotrigine was correlated with lower trough levels of valproate. For dose-corrected concentrations, the connection was much higher statistically, which does not square with findings from the literature. Some authors suggest cutting the first dose of lamotrigine in half since valproate may double its plasma levels. Researchers Kanner et al. found that the amount of valproate given and the steady-state concentration of valproate had no effect on the degree to which lamotrigine clearance was inhibited. Some studies have shown that lamotrigine clearance may be anticipated when taking valproate at 500 mg daily, with decreasing inhibition at lower doses. Unfortunately, similar outcomes were observed in healthy participants who received fairly modest dosages of valproate.

Lamotrigine's trough concentrations were shown to have no link with those of MHD or phenobarbital when we looked at correlations with single inducers of antiepileptic medications such carbamazepine, MHD, and phenobarbital. Patients were given different amounts of AEDs, thus the concentration was adjusted; after that was done, the correlation between carbamazepine and MHD became statistically significant. Oxcarbazepine may produce a subset of CYP and/or UGT isoenzymes with reduced activity. Since MHD, the major metabolite of oxcarbazepine, is mostly cleared by glucuronide conjugation, this may explain the positive link between lamotrigine and MHD. The liver is responsible for the oxidation of carbamazepine, changing it from an epoxide to a diol. This process, which is followed by conjugation with UGT2B7, may account for the shaky connection between lamotrigine and car-borne bamazepine. Carbamazepine and oxcarbazepine may stimulate lamotrigine metabolism, leading to decreased lamotrigine levels. However, in the subsequent phase, carbamazepine/MHD and lamotrigine compete for the same enzymes. This may eventually lead to higher lamotrigine and carbamazepine/MHD concentrations.

Topiramate, a mild inducer, and other drugs whose principal route of elimination is renal excretion, such gabapentin, vigabatrin, and levetiracetam, did not alter the kinetics of lamotrigine, as previously documented. This may be because there weren't enough people in each group to make any meaningful findings.

The intricacy of these systems makes it challenging to foretell the ultimate consequence of these interactions. Drug transporters, They affect the bioavailability and concentrations of many medications, including AEDs, and are found at a wide variety of barriers and organs involved in drug absorption, distribution, and excretion. The complexity of AED pharmacokinetics is further increased by the fact that medications may serve as substrates, inhibitors, or inducers of transporter proteins.

The mechanisms behind drug transport through the direct nasal-to-cerebral pathway are not yet fully understood, despite increasing research into this topic. However, the olfactory and trigeminal pathways are considered primary channels for drug transport from the intranasal cavity to the brain, whereas the systemic circulation and subsequent bridging of the BBB are considered indirect routes. To begin, a brief overview of nasal anatomy relevant to medication absorption through the nasal route is provided. (Figure 3A), followed by a discussion of the known processes underpinning the drug's travel pathways to the brain after intranasal delivery

(Figure 3B).

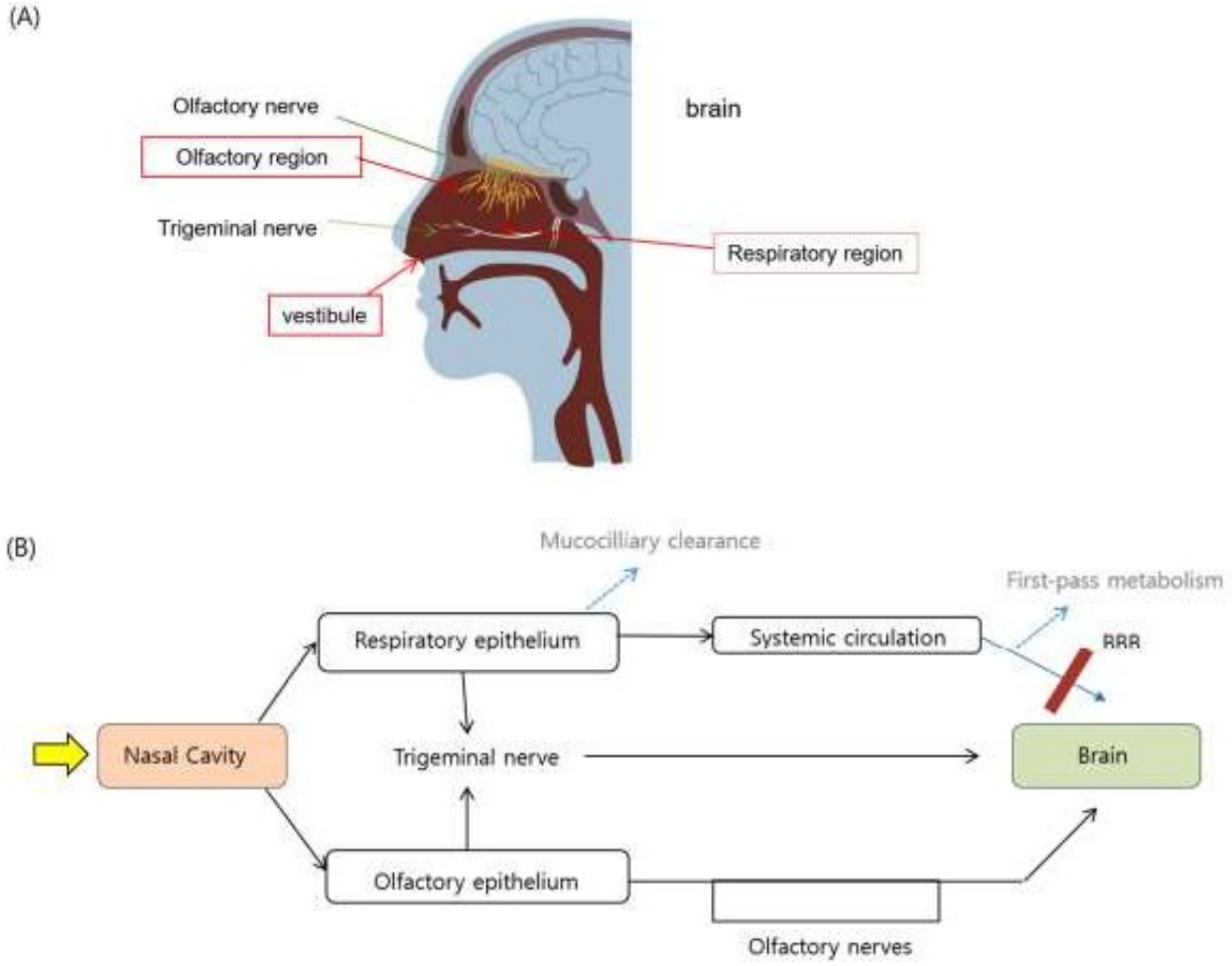

Figure 3. (A) Possible drug delivery structure in the nasal cavity and (B) how drugs might be taken into the brain after being sprayed in the nose.

Liposomes have been developed for the intranasal administration of both hydrophilic and lipophilic medicines. Lipophilic chemicals may cross the blood-brain barrier (BBB) and reach the brain through the olfactory and trigeminal nerves after intranasal administration. Direct nasal absorption is preferred for medications that are hydrophobic or have a high molecular weight since they cannot cross the BBB. For this reason, Table 4 summarizes current work with hydrophilic medicines, while Table 5 does the same with lipophilic/amphiphilic medications.

Table 4. Pharmaceutical lipid formulations optimized for transnasal administration of hydrophilic medicines.

Composition	Particle Size	Zeta Potential	Drug (MW)	Target Disease	In Vivo	Dosing Position	Dosing Volume
DOPC:CHOL:SA	149 nm	+30 mV	GDNF (15,100)	Parkinson's Disease	SD rat	supine	25 μL
DOPC:CHOL:SA	299 nm	+19 mV	ovalbumin (43,000)		SD rat	supine	25 μL
HSPC:CHOL	128 nm	−15 mV	bFGF (16,500)	ischemic stroke	SD rat	supine	~30 μL
EPC:CHOL:DSPE-PEG	112 nm	+3 mV	H102 peptide (1,289)	AD	SD rat		40 μL
soyPC:DHAHAB	142 nm	+6 mV	2-PAM (173)	Organoph-osphorous poisoning	Wistar rat		
EPC:CHOL	166 nm	+11 mV	rivastigmine tartrate (400)	AD	SD rat	supine	~80 μL
EPC:CHOL	40 nm	−48 mV	ferric ammonium citrate (262)	iron deficiency	SD rat	supine	45 μL
soyPC:CHOL (30:0.2)	112 nm	+49 mV	galanthamine hydrobromide (368)	AD	SD rat	prone	40 μL

Table 5. Pharmaceutical lipid formulations optimized for transnasal administration of lipophilic and amphiphilic medicine.

Composition	Size	Zeta Potential	Drug (MW)	Disease	In Vivo	Dosing Position	Dosing Volume
DSPC:CHOL:PEG	102 nm	−28 mV	donepezil (379)	AD	Wistar rat		
DMPC:DMPG	104 nm	NA	fentanyl citrate (336)	opioid analgesic	Rat	POD	20 μL for PK
Phospholipid:CHOL	126 nm	−9 mV	celecoxib (381)	AD	Mice		
soyPC:CHOL, soyPC:CHOL:SA or soyPC:CHOL: DSPE-PEG	90–100 nm	−54, +15, −29 mV	risperidone (410)	Schizophrenia	Wistar rat		50 μL
L-α-PC:SDC or L-α-PC:Span60	380–410 nm	NA	olanzapine (312)	Schizophrenia	Wistar rats	Prostrate	
EPC:CHOL	152 nm	+25 mV	quetiapine fumarate (384)	Schizophrenia	albino mice	Supine	100 μL
EPC:CHOL:α-tocopherol:Omega	192 nm	−15 mV	tacrine hydrochloride (235)	AD			
phospholipid90G: CHOL:Tween80	140 nm	NA	lamotrigine (256)	Epilepsy			

CONCLUSION

In conclusion, we found that increased lamotrigine serum levels occurred at greater concentrations of valproate. As the bulk of these medications' side effects are dose-dependent, doctors should bear this in mind when prescribing them together. Lamotrigine, carbamazepine, and MHD concentrations all showed positive associations, suggesting that when induction was complete, No further drop in lamotrigine concentrations was seen when the dose-corrected concentration of inducers was increased. Given that AED adverse effects are dose-dependent, these results may have therapeutic relevance for AED dosage, and They provide credence to the notion that further measurement of blood levels is the best way to regulate lamotrigine dosage in an individual patient. Our results need to be replicated in research using bigger samples sizes.

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