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INTRANASAL DELIVERY OF ANTIDIABETIC DRUGS

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ABSTRACT

Diabetes is a metabolic disorder defined by higher blood glucose levels in the body generally controlled by antidiabetic agents (oral) and insulin (subcutaneous). To avoid the limitations of the conventional routes such as lower bioavailability and pain at the site of injection in case of parenteral route modified delivery systems are proposed like transdermal, pulmonary and inhalation delivery and among the other delivery systems nasal drug delivery system that shows the advantages such as reduced frequency of dose, higher patient compliance, safety, ease of administration, prolonged residence time, improved absorption of drug in the body, higher bioavailability and stability. This review article discusses the strategies adopted for the delivery of antidiabetic drugs by the intranasal delivery system. The insulin and glucagon-like peptides on experimentation show results of improved therapeutic levels and patient compliance. The drugs are transported by the paracellular route and absorbed through the epithelial tight junctions successfully by utilising different strategies.

KEYWORDS: Diabetes, Intranasal, Desmopressin, Insulin, chitosan, Antidiabetic action.

INTRODUCTION AND BACKGROUND

Drugs are delivered to the systemic circulation via several routes, such as oral, parenteral (intravenous, intramuscular), and in most cases, drugs administered via these routes encounter acidic or enzymatic degradation and may undergo excessive first-pass effect (hepatic metabolism) following administration. Due to these factors, effective doses of drugs sometimes may not reach the systemic circulation, resulting in ineffective treatment. It is therefore required to explore either alternate routes or specialized delivery technologies that can result in improved and effective drug delivery options. The nasal route of drug delivery is one such alternate route that provides access to highly vascularized mucosa, which can be exploited as an interesting site for local drug delivery, systemic drug delivery, and targeted drug delivery (CNS),[1] At the end of the twentieth century, the nasal delivery route became more prominent as an alternative route to treat systemic symptoms such as in cardiovascular indications. The possibility to deliver drugs to the central nervous system (CNS) through nasal pathways remained unexplored until in 1991. William Frey II proposed a patent for a nasal drug delivery method to treat neurological disorders in the brain.

Nasal Drug Delivery Devices

Drug delivery devices have been found to play an important role in ensuring that the entire drug is delivered to the target site in the nasal cavity. It is difficult to precisely deliver the drug to the olfactory region of the human nasal cavity as this region is found high up in the nasal cavity, above the superior conchae. This area is exposed to a very low volume of the air that penetrates the nasal cavity and can result in lower doses of the drug reaching the olfactory region.[2] Some of the novel proprietary devices that have shown significant differences following administering the drug via the nasal route are shown in Table 2.[18-21]

TABLE 2

Company	Device Name
Optinose	Bi-Directional Technology™
Impel NeuroPharma	POD Device
Kurve Technology	ViaNase Technology/Controlled Particle Dispersion (CPD®) Technology Platform

Proprietary Nasal Drug Delivery Devices[22]

ADVANTAGES WITH SYSTEMIC NASAL DRUG DELIVERY

The nasal cavity is covered by a thin mucosa which is well vascularised. Therefore, a drug molecule can be

transferred quickly across the single epithelial cell layer directly to the systemic blood circulation without first-pass hepatic and intestinal metabolism. The effect is often reached within 5 min for smaller drug molecules. Nasal administration can therefore be used as an alternative to oral administration, by crushing or grinding tablets or capsules and snorting or sniffing the resulting powder, providing a rapid onset of effects. If a fast effect is desired or if the drug is extensively degraded in the gut or liver drugs which are poorly absorbed orally can also be given by this route.[3]

LIMITATIONS WITH NASAL DRUG DELIVERY SYSTEMS

Nasal administration is primarily suitable for potent drugs since only a limited volume can be sprayed into the nasal cavity. Drugs for continuous and frequent administration may be less suitable because of the risk of harmful long-term effects on the nasal epithelium. Nasal administration has also been associated with a high variability in the amount of drug absorbed. Upper airway infections may increase the variability as may the extent of sensory irritation of the nasal mucosa, differences in the amount of liquid spray that is swallowed and not kept in the nasal cavity and differences in the spray actuation process.[4] However, the variability in the amount absorbed after nasal administration should be comparable to that after oral administration.

DRUGS FOR NASAL ADMINISTRATION

The area of intranasal medication delivery provides a huge opportunity for research – both for specifically developed pharmaceutical drugs designed for intranasal treatment, as well as for investigating off label uses of commonly available generic medications. Nasal spraysfor local effect are quite common.

Peptide drugs (hormone treatments) are also available as nasal sprays, in this case to avoid drug degradation after oral administration.[5] The peptide analogue desmopressin is, for example, available for both nasal and oral administration, for the treatment of diabetes insipidus.Intranasal insulin is being investigated for treatment of neurodegenerative disorders such as Alzheimer's disease. In ketamine commonly being used for the treatment of breakthrough pain in patients with chronic pain is now becoming an area of significant research interest for the treatment of bipolar disease and major depressive disorder with early results suggesting a strong and prolonged antidepressant effect following a single sub dissociative dose (50 mg) ketamine.[6]

DESMOPRESSIN-ANTIDIABETIC FOR DIABETES INSIPIDUS

Desmopressin is a medication that helps the body's vasopressin receptors.

It has a wide range of clinical applications including nocturnal enuresis and haemophilia.

While this drug is reasonably safe to use, there are some negative effects to be aware for patients who are using it, as well as particular contraindications that limit the population who can take it.

This activity goes over the indications, mode of action, contraindications, and side effects of the medication.

It will also look into how to properly monitor patients on desmopressin, as well as the role of the inter professional team in improving the drugs outcomes.[7]

OBJECTIVES

Determine when desmopressin should be used in a patient.

Desmopressin's method of action should be described.

Examine desmopressin's potential side effects.

Summarize the role of an integrated inter-professional team in the management of desmopressin treated patients.[8]

INDICATIONS

Desmopressin (1-deamino-8-D-arginine vasopressin) is a synthetic analouge of vasopressin, aka antidiuretic hormone, developed in 1977 and used to treat a variety of medical conditions such as nocturnal polyuria, haemophilia-A, diabetes insipidus, Willebrand disease, uremic bleeding, as well as many off-label uses such as an adjunct with hypertonic saline frequent disorder that affects nearly solely children and respond to both oral and intranasal desmopressin therapy.

Adults who wake up more than twice a night to voidmay be prescribed desmopressin.

Polyuria and polydipsia are commonly symptoms of diabetes insipidus (DI), which can be caused by avariety of different illnesses.

Nephrogenic and central diabetes insipidus are the two main kind of diabetes insipidus The failure of the kidneys to respond to antidiuretic hormone causesnephrogenic diabetes insipidus, which can develop as a result of long-term lithium use or overdose, as well as a variety of other illnesses that alter the kidneys' innate capacity to operate optimally.[9]

Central diabetes insipidus is caused by the hypothalamus' inability to produce ADH, which can be caused by CNS or head trauma, CNS cancers such as craniopharyngioma or germinoma, or the degradation of ADH by placental e nzymes vasopressinase.

Water deprivation does not allow the urine to concentrate optimally in both central and nephrogenic diabetes insipi dus, resulting in a prolonged and continuous outflow of h ypotonic urine.

Desmopressin administration can be used to differentiate between central and nephrogenic nephropathy.

Desmopressin has also been utilized in trauma resuscitation and post-surgically to receive haemostasis. Several animal studies have demonstrated that desmopressin is useful in treating severe coagulopathy in injured or post-surgical patients.[10]

Modes

Standard

Mechanism of Action Desmopressin is a selective vasopressin V2 receptor agonist present throughout the collecting ducts and distal convoluted tubules of the kidneys. The V2 receptor is a Gs-protein coupled receptor, which, when activated, results in a signalling cascade of adenyl-cyclase, prompting an increase in cyclic adenosine monophosphate (cAMP) in the renal tubule cells, ultimately resulting in increased water permeability. This activity leads to a decrease in urine volume and an increase in urine osmolality.[11] The signalling cascade resulting in the production of cyclic adenosine monophosphate also induces exocytosis of von Will brand factor and factor VIII from its storage sites, as well as the Weibull-Palade bodies and the alpha granules of platelets. Von Will brand factor functions as the first step in thrombogenesis, acting as the bridging factor of the Gp1b factor on platelets to the sub endothelial collagen following tissue injury. By utilizing synthetic ADH analogues, such as desmopressin, the clotting.

MECHANISM OF ACTION

Desmopressin is a selective vasopressin V2 receptor ago nist that is found in the kidneys' collecting ducts and dist al convoluted tubules.

The V2 receptor is a Gs-protein coupled receptor that, when activated, triggers an adenyl-cyclase signalling cascade in the renal tubule cells, resulting in an increase in cyclic adenosine monophosphate (cAMP) and increased water permeability.[12]

Urine volume decreases and urine osmolality rises as a re sult of this exercise.

Exocytosis of von Willebrand factor and factor VIII from their storage locations, as well as the Weibel-Palade bodies and alpha granules of platelets, is induced by the signalling cascade that results in the synthesis of cyclic adenosine monophosphate.

Von Willebrand factor is the initial step in the thromboge nesis process, acting as a bridge factor between platelets and subendothelial collagen after tissue injury.

Synthetic ADH analogues, such as desmopressin, can hel p with clotting.[13]

Modes

Standard

Administration Desmopressin can be administered intravenously, as a subcutaneous injection, as an intranasal spray, and, most recently, as a dissolvable sublingual strip. The tablet form has been discontinued in many countries in favour of the intranasal and sublingual forms due to the latter's superior bioavailability. The administration of intravenous and subcutaneous dose forms of the drug are predominantly in the hospital setting. Dosing for both is 0.3 micrograms/kg. Peak blood concentration after intravenous administration occurs within 30 to 60 minutes and after subcutaneous administration within 60 to 90 minutes. The intranasal form of vasopressin is frequently a choice when administration occurs at home. Each spray typically dispenses 150 micrograms. The intranasal dosage is directly proportional to the patient's weight, with patients weighing less than 50 kg prescribed one spray, or 150 micrograms, and patients over 50 kg prescribed 2 sprays, or 300 micrograms, every 12 to 24 hours.[14]

Administration

Desmopressin is available as an intravenous injection, a s ubcutaneous injection, an intranasal spray, and a dissolva ble sublingual strip.

Due to the greater bioavailability of the intranasal and sublingual versions, the tablet form has been phased out in several countries.

The drug's intravenous and subcutaneous dosage forms a re typically administered in a hospital setting.

The dosage for both is 0.3 micrograms per kilogramme.

After intravenous treatment, peak blood concentration ta kes 30 to 60 minutes, while subcutaneous administration takes 60 to 90 minutes.

When vasopressin is administered at home, the intranasal version is frequently chosen.[15]

Negative effects

Hyponatremia is the main desmopressin side effect to ke ep an eye on.

Because desmopressin raises urine concentration, it can c ause systemic hyponatremia, which has a physiology sim ilar to that of inappropriate antidiuretic hormone syndro me.

The hyponatremia generated by this medicine can trigger seizures in certain people.

Headaches, tachycardia, and facial flushing are some of t he minor side effects that may occur in some patients.[16]

Desmopressin therapy has been linked to strokes and my ocardial infarctions in some people.

These situations, however, were uncommon, and it is im possible to say with certainty that desmopressin played a direct role in these cases.

Contraindications

Except for symptomatic hyponatremia requiring intensive therapy and the risk of osmotic demyelinating syndrome, hyponatremia is an absolute contraindication to desmopressin administration. Desmopressin works predominantly in the nephron, thus it's not recommended for people who have kidney problems.

Renal function declines with age, thus caution is advised when providing this medication to the elderly. This medicine should also be avoided in younger kids, particularly those under the age of two, because restricting water and fluids in these individuals is challenging.

Furthermore, this medicine is ineffective in individuals with type 3 von Will brand disease; as a result, these patients should not take it.
Finally, desmopressin should not be given to patients with thrombocytopenic purpura since it can cause a thrombotic event.[17]

Monitoring
The majority of patients tolerate desmopressin effectivel y.
There are a few occasions where patients must be monito red for pharmacological side effects.
Hyponatremia in desmopressin-
treated patients must be closely monitored.
Nausea, disorientation, and impaired mental status are all symptoms of hyponatremia.
Patients should be evaluated for diminishing renal functi on as they become older, as the therapeutic index and cle arance of the medicine will change depending on renal fu nction.

Toxicity
An overdose of desmopressin has no recognised antidote.
Water intoxication is the most dangerous complication of an overdose.
In some cases, this disease would cause a delayed loss of consciousness and convulsions.
Patients must be admitted to the intensive care unit right away to be monitored and have their electrolytes correcte d.

INSULIN-ANTIDIABETIC FOR TYPE-1 DIABETES MELLITUS
Background: Insulin (INS) has been used in the treatment of diabetes mellitus. Due to its large molecular weight and short half-life, it has been usually administered subcutaneously accompanied with side effects such as the possibility of hypoglycemia episodes, weight gain and inadequate post-meal glucose control. Objective: In order to overcome these limitations, alternative delivery routes of insulin are expected to provide better safety and compliance for the patient. Non-invasive insulin delivery system represents one of the most challenging goals for pharmaceutical industry. Nasal insulin delivery has been extensively studied as an alternative to subcutaneous injection for the treatment of diabetes. The pharmacokinetic profile of nasal insulin is similar to that obtained by intravenous injection. Result & conclusion: This review discusses the most recent developments in nasal insulin administration technology.[18] Firstly, the structure and physiology of the nasal cavity are introduced. Then, the advantages and disadvantages of nasal administration are discussed. Next, the methods of enhancing nasal insulin absorption and the dosage forms for insulin nasal administration are described. Furthermore, new therapeutic indications of nasal insulin administration were also investigated. Finally, the future development and respective technology of nasal insulin administration are prospected.

NASAL DELIVERY OF INSULIN USING BIO ADHESIVE CHITOSAN GELS
The intranasal route for drug administration probably is one of the most attractive routes for distributing drugs to the systemic circulation. This is because of serious drawbacks of parenteral route in chronic therapy, rich vascularization of nasal route, and hence rapid absorption of drugs, highly permeable tissue, fast onset of action, ease of administration, and familiarity to the population at large, utility of chronic medication, and circumvention of first-pass metabolism. Recently, however, evidence has suggested that this route may be useful for labile drugs that are only administered parentrally. For example, the nasal administration of insulin to dogs resulted in a significant increase in blood immunoreactive insulin levels with remarkable hypoglycaemia. Moreover, the nasal absorption of insulin was enhanced by the addition of absorption enhancers such as surfactants to the insulin solution. Meanwhile, the rectally administered aqueous gel base of polyacrylic acid was found to improve the absorption of peptide hormones such as insulin and calcitonin.

Chitosan is a copolymer of β-(1 → 4)-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose. This polycationic biopolymer is generally obtained by alkaline deacetylation from chitin, which is the main component of the exoskeleton of crustaceans, such as shrimps. The main parameters influencing the characteristics of chitosan are its molecular weight and degree of deacetylation, representing the proportion of deacetylated units. These parameters are determined by the conditions set during preparation. Moreover, they can be further modified. For example, the degree of deacetylation can be lowered by reacetylation and molecular weight can be lowered by acidic depolymerisation.

It is a suitable biodegradable matrix for the production of gels owing to its biocompatibility, biodegradability. bio adhesive properties, and particularly the possibility of being covalently cross-linked through its amino groups.[19] This last quality allows its stabilization as a matrix for controlled release systems.

The objective of our-work was to study the nasal absorption of insulin from chitosan gel as a bio adhesive polymer, which can increase the residence time of the drug and act as an absorption promoter. Except the use of chitosan as a 0.5% solution that has caused seven times higher AUC of insulin in sheeps, to our knowledge there is no other report about the use of chitosan gel for nasal delivery of insulin.

On the other hand chitosan itself is a bio adhesive polysaccharide that can prolong the contact time of the drug with the nasal mucosa. In addition to mucoadhesion, chitosan also has been shown to enhance drug absorption via the Para cellular route through neutralization of fixed anionic sites in the tight junctions

between mucosal cells. Morimoto et al. 1used a polyacrylic acid gel for nasal delivery of insulin. This gel showed maximum hypoglycemic effects at 30 min. Recently, Najafabadi et al. reported the production of an insulin carbopol gel spray that produced a significant hypoglycemic response in rabbits. The bioavailability of insulin from this nasal gel formulation was 20.6% compared with the i.v Injection indicates that after nasal administration of M2E gels, insulin blood concentration reached maximum level after 1 hr and its duration lasted up to 4 hr. The results of Table 4 indicate a 63% reduction in blood glucose concentration with a 46% bioavailability of insulin from this gel that seems promising.

Intranasal insulin and its efficacy in Diabetes mellitus

Insulin has been in use for the treatment of DM for nearly 100 years now. During this time, due to rigorous research and development, everything from the delivery system to the molecule itself has undergone a drastic change.

The cornerstone of conventional insulin therapy is the subcutaneous method, which requires single or many daily injections. Despite the introduction of user-friendly insulin pens, injectable therapy does not hold the best patient compliance. In addition, despite constancy in the parenteral dose regimen and injection site, metabolic variability in glycemic control exists in most insulin-dependent diabetics. Efforts today are being made to design insulin delivery systems that replicate the physiological release of insulin in the body, an advantage thus offered by the intranasal delivery system.

A robust selection of oral and injectable hypoglycemics and insulin analogues are already available. Intranasal insulin, other than the cognitive benefits, offers slight advantages.

In type 2 diabetics, it was found that intranasal insulin did not only affect fasting and postprandial blood glucose levels but did so in a way that simplified dosing too. Frauman et al. showed that a single intranasal dose of 30 units of porcelain insulin was an effective alternative to oral hypoglycemics, avoiding many of the issues that come with their use in clinical practice. Moreover, a second dose may be administered 30 minutes after a meal for additional control. The only drawback is that substantial doses are needed compared to subcutaneous injections, ruling it out as a realistic alternative, at least in its current form. Larger doses would also mean a 5-10 times higher cost than conventional therapy to the patient, a problem that may be circumvented using the new once a week dispenser. With its somewhat poor bioavailability and amputated ability to normalize glucose levels on its own, clinicians have instead proposed using intranasal therapy as an additive to NPH insulin rather than a replacement, particularly after meals. Moreover, this dependency on a significant basal insulin level may contribute to Type 1 DM patients.[20]

ADVERSE EFFECTS AND LIMITATIONS OF INTRANASL INSULIN

Adverse effects /safety profile

Even though intranasal insulin is well tolerated by most individuals. it can cause minor adverse effects. In various studies, adverse effects related to the nose(rhinitis, minimal nose bleed, soreness, dripping, sneezing), upper respiratory tract infections, headaches, dizziness, weakness, hypoglycemia, fall, rash, gastrointestinal symptoms are reported. Rhinitis followed by other local side effects (nose related symptoms) is most commonly reported, which could be due to the mode of drug administration. The risk of hypoglycemia which is a significant concern with insulin, is negligible with the intranasal route.

Limitations

Although intranasal insulin has a better safety profile, the most significant limitation is the bioavailability of the drug, which is less than 1% through nasal administration, contributing by the low permeability of the nasal mucosa, rapid mucociliary clearance of the administered drug and the possible enzymatic degradation of the drug. The low permeability is primarily due to the large molecular size of insulin. The nasal cavity aminopeptidases (proteolytic enzymes) are the most common enzymes responsible for the degradation. The exopeptidases and the endopeptidases cleave the peptides at N, C terminals and the internal peptide bonds, respectively. However, In a review, Duan and Mao described various new strategies to improve the intranasal absorption of insulin. The nasal absorption or transport of insulin can be improved by using water-insoluble powders with nasal absorption enhancers. The mucociliary clearance can be prevented by using mucoadhesive /bio adhesive drug delivery systems. The proteolytic degradation of the drug can be prevented by the chemical modification of the proteins, using proteolytic enzymes degraders. However, these adsorption enhancers, bio adhesive and water-insoluble excipients should be screened furthermore for the safety profile and the effectiveness in increasing the nasal bioavailability of insulin.

Metformin-Antidiabetic for first-linemedication for the treatment of type 2 diabetes,particularly in people who are overweight It is also used in the treatment of polycystic ovary syndrome It is not associated with weight gainand is taken by mouth.It is sometimes used as an off-label augment to attenuate the risk of weight gain in people who take antipsychotics as well as phenelizine.

REFERENCES

1. Frey W H.III. Neurologic agents for nasal administration to the brain [Internet]. 1991. Available from:

(https://patentscopwipo.int/search/en/detail.jsf?docId =WO1991007947&tab=PCTBIBLIO).
2. Axel R. Scents and sensibility: a molecular logic of olfactory perception (Nobel lecture). Angew Chem Int Ed, 2005; 44: 6110–27.
3. Crisler R, Johnston NA, Sivula C, Budelsky CL. Functional anatomy and physiology. Lab Rat [Internet]. Elsevier; 2020 [cited 2020 Jul 13]. p. 91–132. Available from:https://linkinghub.elsevier.com/retrieve/pii/B9 780128143384000040.
4. Mygind N, Dahl R. Anatomy, physiology and function of the nasal cavities in health and disease. Adv Drug Deliv Rev, 1998; 29: 3–12.
5. Harkema JR, Carey SA, Wagner JG. The nose revisited: a brief review of the comparative structure, function, and toxicologic pathology of the nasal epithelium. Toxicol Pathol, 2006; 34: 252–69.
6. Chamanza R, Wright JA. A review of the comparative anatomy, histology, physiology and pathology of the nasal cavity of rats, mice, dogs and non-human primates. Relevance to inhalation toxicology and human health risk assessment. J Comp Pathol, 2015; 153: 287–314.
7. Jones N. The nose and paranasal sinuses physiology and anatomy. Adv Drug Deliv Rev, 2001; 51: 5–19.
8. Henson B, Drake TM, Edens MA. Anatomy, head and neck, nose sinuses. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2020 Jul 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK513272/
9. Stamegna J-C, Girard SD, Veron A, Sicard G, Khrestchatisky M, Feron F, et al. A unique method for the isolation of nasal olfactory stem cells in living rats. Stem Cell Res, 2014; 12: 673–9.CAS PubMed Article Google Scholar.
10. Girard SD, Devéze A, Nivet E, Gepner B, Roman FS, Féron F. Isolating nasal olfactory stem cells from rodents or humans. J Vis Exp [Internet]. 2011 [cited 2020 Nov 30]; Available from: http://www.jove.com/details.php?id=2762.
11. Ozgönenel B, Rajpurkar M, Lusher JM, How do you treat bleeding disorders with desmopressin? Postgraduate medical journal. 2007 Mar [PubMed PMID: 17344569].
12. Fein S, Herschkowitz S, Low-Dose Desmopressin Nasal Spray and FDA Approval. JAMA. 2017 Sep 19; [PubMed PMID: 28975296].
13. Wiśniewski K, Qi S, Kraus J, Ly B, Srinivasan K, Tariga H, Croston G, La E, Wiśniewska H, Ortiz C, Laporte R, Rivière PJ, Neyer G, Hargrove DM, Schteingart CD, Discovery of Potent, Selective, and Short-Acting Peptidic V{sub}2{/sub} Receptor Agonists. Journal of medicinal chemistry, 2019 May 23 [PubMed PMID: 31022340]
14. Desmopressin (Nocdurna and Noctiva) for nocturnal polyuria. The Medical letter on drugs and therapeutics, 2019 Mar 25; [PubMed PMID: 31022158]
15. Konkle BA, Huston H, Nakaya Fletcher S, Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, Hemophilia A GeneReviews®, 1993 [PubMed PMID: 20301578].
16. Di Iorgi N, Morana G, Napoli F, Allegri AE, Rossi A, Maghnie M, Management of diabetes insipidus and adipsia in the child. Best practice & research. Clinical endocrinology & metabolism. 2015 Jun.
17. Chanson P, Salenave S, Treatment o neurogenic diabetes insipidus. Annales d'endocrinologie, 2011 Dec [PubMed PMID: 22071315].
18. Ott M, Forssén B, Werneke U, Lithium treatment, nephrogenic diabetes insipidus and the risk of hypernatraemia: a retrospective cohort study. Therapeutic advances in psychopharmacology, 2019; [PubMed PMID: 31007893].
19. Alharfi IM, Stewart TC, Foster J, Morrison GC, Fraser DD, Central diabetes insipidus in pediatric severe traumatic brain injury. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 2013 Feb [PubMed PMID: 23314181].
20. Leroy C, Karrouz W, Douillard C, Do Cao C, Cortet C, Wémeau JL, Vantyghem MC, Diabetes insipidus. Annales d'endocrinologie. 2013 Dec; [PubMed PMID: 24286605]