DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(11), 1419-1436 (1991)

USE OF CHEMICAL ENHANCERS FOR NASAL DRUG DELIVERY

De Ponti R., Lardini E.
New Drug Delivery Systems, Galenical R&D,
Farmitalia Carlo Erba srl,
24 via Imbonati, I-20159 MILANO MI - ITALY

The use of intranasal route for administration of drugs is known since many years <1;2>.
The possibilities of intranasal route are recently growing their interest, for the development that new proteins and peptides have in therapeutic.
The nasal mucosa is particularly attractive for the delivery of peptides and proteins because of both its low enzymic activity <3> and the avoiding of the metabolic first-pass effect <3>. The two more important features related to nasal drug delivery are (A) the permeability of nasal mucosa (the nasal mucosa is normally moderately permeable to water-soluble compounds, comparable with ileum or gallbladder, while it is higher than other mucosa like the vaginal one <4;5>) and (B) the so-called nasal clearance, due to the coordinated movement of cilia <6>.

Different physiological and pathological states can determine different nasal clearance rates: [6;7] a common cold increases the nasal clearance in a dramatic way, and the same occurs following polypectomy [8].

Physiologic factors are responsible for circadian rhythm and, in order to have no influence of such effects on the nasal absorption, some authors have proposed that nasal insufflation has to be performed in both the nostrils with two insufflations per nostril, one towards the upper direction and the other toward the bottom of the nostril [9].

The major efforts of scientists to improve nasal absorption are addressed to the use of substances acting as absorption promoters, otherwise called absorption enhancers or penetration enhancers.

Absorption enhancers can be divided in many different classes: a first classification is between the chemical and physical enhancers. Generally speaking, chemical enhancers act by destructuring the nasal mucosa, very often in an irreversible way. Physical enhancers have the effect to slow the nasal clearance generally forming a gel. This last effect is reversible as the nasal clearance is impaired only for a limited period, until the gel is swallowed.

Among chemical enhancers can be named chelating agents, fatty acids, bile acid salts and other surfactants, fusidic acid, lysophosphatides, cyclic peptide antibiotics, preservatives, carboxilic acids (ascorbic acid, amino acids), glycyrrhetinic acid, O-acylcarnitine; pH and osmolarity can also play an important role and should be considered in the chemical enhancers class.

Among the chelating agents can be named sodium edetate, citric acid, salicylates, N-acylderivatives of collagen and enamines (N-amino acyl derivatives of β-diketones). Chelating agents interfere with the ability of calcium ions to maintain the dimension of the intercellular space, permitting the paracellular transport of peptides and proteins otherwise excluded from this pathway [10]. Moreover, calcium is believed to play a vital role in the regulation of ciliary activity [11]. Sodium edetate (0.1%) is currently used in two formulations marketed in Italy and citrates are used in four formulations marketed in Italy. Irreversible damage of ciliated epithelium due to sodium edetate at a concentration of 0.1% is reported [11] for this reason the use of sodium edetate (0.05%) is recommended [12] in combination with benzalkonium chloride (0.01%) to provide the preservation of nasal preparations with the least harmful action [12].

Fatty acid and their derivatives are also used as enhancers, and are often used with glycerides and lecithins in inhalation aerosols for technical reasons (lubrication). These surfactants are non-volatile liquids dissolved in the propellants and they will appear in the generated aerosol together with the drug particles [13].

C8 and C10 chain length mono- and di-glyceride extracts of coconut oil were found to enhance enteral, oral and rectal absorption of ceftriaxone [14].

Oleic acid and monoolein are capable of increasing membrane fluidity either by creating disorder in domain in the membrane or by facilitating the leaching of

proteins from the membrane [15]. Mixed micelles composed of monoolein or unsaturated fatty acids markedly enhanced the absorption of streptomycin in the large intestine. It was found that taurocholic acid depressed amino acid absorption but the addition of monoolein restored amino acid absorption to normal [16].

Bile acid salts, also compounds in the class of absorption enhancers, can be divided in two sub-classes, unconjugated and conjugated bile acid salts, in which dihydroxy and trihydroxy bile acid salts can be encountered:

3α,12α-dihydroxy-5β-cholanoates, e.g.:
Na deoxycholate
Na glycodeoxycholate
Na taurodeoxycholate

3α,7α,12α-trihydroxy-5β-cholanoates, e.g.:
Na cholate
Na glycocholate
Na taurocholate

The more efficient enhancer among bile acid salts studied was the more hydrophobic, Na deoxycholate [17]. Bile salts may act as absorption enhancers for bioactive materials (like insulin) by one or more of the following mechanisms:
a) producing high juxtamembrane concentrations of insulin monomers via solubilization in mixed bile salt micelles;

b) forming reversed micelles within nasal membranes, though which bioactive materials (e.g., insulin) monomers can diffuse from the extracellular space; the addition of 0.5% Na deoxycholate to the mucosal bathing solution in a dog/rat model [18] caused a rapid, four- to five-fold increase in permeability to sucrose or cholecystokinin octapeptide. The observed increase in permeability was bidirectional, was not reversed by washing and accompanied by histological evidence of extensive loss of the surface epithelium layer: these results indicate that bile salts enhance nasal permeability by removing the epithelium cells, which constitute a major permeability barrier, rather than causing a chemical modification of the mucosal cells. This argues against the use of bile salts to enhance nasal drug absorption in patients;

c) reducing the viscosity of the mucus layer adhering to all mucosal surfaces, thereby facilitating peptide and protein diffusion towards the membrane surface [19];

d) having the ability to inhibit proteolytic enzyme activity in the membrane [20].

Suitable methods to study the ability to inhibit proteolytic enzyme activity in the membranes were described by Hanson et al.[21].

A detailed study on Na deoxycholate, Na glycodeoxycholate, Na taurodeoxycholate, Na cholate, Na glycocholate and Na taurocholate as enhancers for gentamycin transnasal administration was conducted [22] on both promoters characteristics and adverse local reaction of bile salts (ciliotoxicity as ciliary beat frequency related to mucus transport time [23]).

Both Gordon [17] and Duchateau [22] found that the more hydrophobic was the bile salt the higher was the enhancing effect.

Bile salts (1% w/v) were also compared referring to their promoting activity by Hirai [24], finding a less dramatic difference in effect among them.

According to Gordon the reason for that finding may be related to the use of commercial preparations of bile salts, which often are contaminated with other closely related, possibly more hydrophobic, species. Another reason may be a different experimental design. According to Gordon, Hirai and co-workers allowed insulin and bile salt solutions to have prolonged contact with the nasal mucosa of rats after occlusion of the anterior nostrils: hence, only cumulative decreases in blood glucose were observed.

Thus, if maximal insulin transport varied with different bile salt species, the experimental design employed by Hirai would have obscured this effect.

The problem of purity of bile acid salts was recognized by Moses [25], who used highly purified bile acid salts.

To overcome the problems put in evidence by Gordon regarding the Hirai's model, it must be pointed out that new rat-model techniques were described following and improving the Hirai's one, for example the Fischer's model [26].

Other surfactants than the bile salts were used as nasal enhancers, for example saponin (a glycoside), surfactin (a peptidelipin), and laureth-9 (a non-ionic detergent, polyoxyethylene-9 lauryl ether) [24;27].

Polyoxyethylated non-ionic surfactants,interfer with the ability of calcium ions to maintain the dimension of the intercellular space, thereby permetting the paracellular transport of peptides and proteins <28>. Laureth-9 shows one of the highst erythrocyte hemolysis effects <20;29> as well as one of the higher effects on protein release from the nasal mucosa among enhancers <20>. Laureth-9 (1% w/v) has a "destructing action on the mucosal lining which included multifocal necrosis, inflammation and exudation, and in some regions, complete removal of epithelial monolayer" <30>.

Fusidic acid and its derivatives were described as nasal enhancers by Longenecker <29;31>.

Na tauro 24,25-dihydrofusidate (STDHF) is the most extensively studied among the derivatives of fusidic acid, the latter being originally developed in 1962 by Leo Pharmaceutical as an antibiotic (Na fusidate is a fungal metabolite isolated from the fermentation products of Fusidium coccineum).

STDHF has no antibiotic activity, it is not mutagenic, non-irritating to rabbit skin, eye and nasal cavity in acute test: STDHF failed to show any local or systemic lesions associated with the enhancer after thirty day intranasal toxicity studies involving 3 administrations per day in both rats and dogs at doses up to 10% (w/v). STDHF and SGDHF (glyco-) are at least 5-fold less lytic (rabbit erythrocytes lysis, see ref. 29) than Na deoxycholate and 100-fold less lytic than laureth-9. The difference in toxicity between bile salts and STDHF is not explained, but it seems valuable to note that STDHF has a plane structure, which is not the case of bile salts.

Lysophosphatides were recently used as nasal enhancers, in particular L-α-lysophosphatidylcholine <32> that is a known modifier of mucus structure and properties, decreasing viscosity, decreasing elasticity and increasing Na^+ flux. <19;33;34>.

Another nasal enhancer is reported to be a cyclic peptide antibiotic like bacitracin, used to promote absorption of two GHRH analogues in rats <35>.
Bacitracin is a mixture of 9 cyclic peptides obtained from Bacillus subtilis, the pure Bacitracin A (from HPLC purification) was found less effective than the mixture.

Very recently <11> it was reported that some preservatives (like methyl p-hydroxybenzoate (0.02%), propyl p-hydroxybenzoate (0.02%), chlorbutol, chlorocresol, benzalkonium chloride (0.01%), chlorexidine and organo-mercuric compounds), when used in nasal formulations, slow or even stop the mucociliary clearance.
The effects of methyl p-hydroxybenzoate, propyl p-hydroxybenzoate and chlorbutol seem reversible. The action of some preservatives toxicity can add some other difficulties to nasal formulations and these effects of preservatives normally used in solutions should be evaluated. Benzalkonium chloride (0.01%) is used in four formulations and Methyl p-hydroxybenzoate (0.13%) and propyl p-hydroxybenzoate (0.02%) are used in two formulations on the Italian market.

The use of organic acids like ascorbic acid, and basic amino acids and/or their salts was also reported, together with water-absorbing solid bases [36].

Glycyrrhetinic acid, the aglycone of glycyrrhizin, was used as nasal enhancer together with sodium glycinate, glutamate or aspartate, to deliver insulin and Human Growth Hormone [37]. It is known that glycyrrhetinic acid gives, after chronic administration, a clinical iperaldosteronism syndrome. Glycyrrhetinic acid (2%) is used in two formulations on the Italian market.
Recently glycyrrhizin ability in destructuring dipalmitoylphosphatidylcholine (DPPC) bilayer was reported [38] this can partially supply a mechanism for the absorption promoting action of glycyrrhetinic acid, as the main interaction of glycyrrhizin with the DPPC bilayer is mainly due to the triterpene ring and not to the glucuronic acid in the glycyrrhizin structure [38].

O-acylcarnitine derivatives (octanoyl carnitine, lauroyl carnitine, palmitoyl carnitine) were recently proposed for chemicaly enhancing of natural absorption of calcitonin without irritation of the nasal mucosa [39].

Other important factors for enhancing the absorption in nasal delivery are the pH and osmolarity. It was found that secretin (a hormone secreted in GI tract and clinically used for the treatment of duodenal ulcers) was best absorbed at pH 2.94 and in 0.462M NaCl solution. Histological studies [40] revealed structural

changes of epithelium cells of the nasal mucosa at pH 2.94, and shrinkage of epithelium cells was observed when a 0.462M NaCl solution was used.
Shrinkage of epithelium cells can be the mechanism of action associated with the intranasal use of water-absorbable water-swellable powders which gelify into the nasal mucosa surface <32;41;42;43>.
The influence of a gel on slowing nasal clearance is well established too <44;45>.

Alternatively, new methods to deliver drugs through the nasal route, related to the rationale of using systems containing phospholipids able to become upon administration, natural constituents of the mucosa, were recently described, ranging from liposomes <46> to microemulsions <47>.

As a matter of fact, the most important drawback for the use of chemical nasal enhancers is the possibility of toxic effects that, after chronic administration causes irreversible damages, to the nasal mucosa <11; 12; 18; 23; 31; 40; 48; 49; 50>.
Even if good toxicological results were obtained with STDHF, <51> it still remain the problem to carry on activities addressed to the identification of new, possibly non-toxic enhancers.

References

<1> Butler D.B., Ivy A.C., "Method of Application of Drugs to the Nasal Mucosa", Arch. Otolar., 39 (2), Feb.(1944).

<2> Hankiss J., Hadhazy Cs., "Resorption Von Insulin Und Asthmolysin Von Der Nasenshcleimhaut", Acta Med. Sci. Hung., 12, 107-114,(1958).

<3> Colaizzi J.L., "Pharmacokinetics of Intranasal Drug Administration" in "Transnasal Systemic Medications", eds. Chien Y.W. and Chang S.F., Elsevier (1985).

<4> "Delivery Systems for Peptide Drugs", eds Davis S.S., Illum L., Tomlinson E., Plenum Press (1987), page 98.

<5> Chan R.L., et al., "Absorption and Metabolism of Nafarelin, a Potent Agonist of Gonadotropin-Releasing Hormone", Clin. Pharmacol. Ther., 275-282, Sept.(1988).

<6> Proctor D.F., "Nasal Physiology in Intranasal Drug Administration", in "Transnasal Systemic Medications", eds Chien Y.W. and Chang S.F., Elsevier (1985).

<7> Proctor D.F., "The Upper Airways. I. Nasal Physiology and Defence of the Lungs", Am. Rev. Respir. Dis., 115, 97-129,(1977).

<8> Lee S.W., et al., "Nasal Sprays and Polyps", Nuclear Medicine Comm., 5, 697-703,(1984).

<9> Mygind N., "Aerosol Distribution in the Nose", Rhinology, XVI, 79-88,(1978).

<10> Lee V.H.L., "Enzymatic Barriers to Peptide and Protein Absorption and the Use of Penetration Enhancers to Modify Absorption", in "Delivery Systems for Peptide Drugs", Plenum, New York,(1986).

<11> Batts A.H., "The Effect of Some Preservatives Used in Nasal Preparations on Mucociliary Clearance", J. Pharm. Pharmacol., 41, 156-159,(1989).

<12> Hermens A.J.J., Merkus W.H.M., "The Influence of Drugs on Nasal Ciliary Movement", Pharmaceutical Research, 4(6), 445-449,(1987).

<13> Moren F., "Dosage Forms and Formulations for Drug Administration to the Respiratory Tract", Drug Development Ind. Pharm. 13, 691-728,(1987).

<14> Beskid G., et al., " Enteral, oral, and rectal absorption of ceftriaxone using glyceride enhancers", Chemotheraphy, 34, 77-84,(1988).

<15> Muranushi, N., Nakajima, Y., Kinugawa, M., Muranishi, S.and Sezaki, "Mechanism for the inducement of intestinal absorption of poorly absorbed drugs by mixed micelles. II. Effect of the incorporation of various lipids on the permeability of liposomal membranes", Int. J. Pharm., 4, 281-290,(1980).

<16> Dimagno, et al., " Effect of bile acids, lecithin and monoolein on amino acid absorption from the

human duodenum ", Proc. Soc. Exp. Biol. Med., 154, (3), 325-330,(1977).

<17> Gordon G.S., et al., "Nasal Absorption of Insulin: Enhancement by Hydrophobic Bile Salts", Proc. Natl. Acad. Sci. U.S.A., 82, 7419-7423,(1985).

<18> Hersey S.J. and Jackson R.T., "Effect of Bile Salts on Nasal Permeability in Vitro", J. Pharm. Sci., 76 (12), 876-879,(1987).

<19> Martin G.P., et al., "Direct Effects of Bile Salts and Phospholipids on the Physical Properties of Mucus", Gut, 19, 103-107,(1978).

<20> Hirai S., et al., "Mechanism for the Enhancement of the Nasal Absorption of Insulin", Int. J. Pharm., 9, 173-184,(1981).

<21> Hanson M., et al., "Intranasal Delivery of the Peptide, Salmon Calcitonin" in "Delivery Systems for Peptide Drugs", eds. Davis S.S., Illum L., Tomlinson E., Plenum Press,(1987).

<22> Duchateau G.S.M.J.E., et al., "Bile Salts and Intranasal Drug Absorption", Int. J. Pharm., 31, 193-199,(1986).

<23> Duchateau G.S.M.J.E., et al., "Correlation between Ciliary Beat Frequency and Mucus Transport Rate in Volunteers", Laryngoscope, 95, 854-859,(1985).

<24> Hirai S., et al., "Effect of Surfactants on the Nasal Absorption of Insulin in Rats", Int. J. Pharm., 9, 165-172, (1981).

<25> Moses A.C., et al., "Insulin Administered Intranasally as an Insulin-Bile Salt Aerosol. Effectiveness and Reproducibility in Normal and Diabetic Subjects", Diabetes, 32, 1040-1047, (1983).

<26> Fischer A.N., "The Effect of Molecular Size on the Nasal Absorption of Water-Soluble Compounds in the Albino Rat", J. Pharm. Pharmacol., 39, 357-362,(1987).

<27> Duchateau G.S.M.J.E., et al., "Influence of some surface-active agents on nasal absorption in rabbits", Int. J. Pharm., 39, 87-92, (1987).

<28> Sakai. K., Kutsuna, T.M., Nishino, T., Fujihara, Y. and Yata., "Contribution of calcium ion sequestration by polyoxyethylated non-ionic surfactants to the enhanced colonic absorption of p-aminobenzoic acid",J. Pharm. Sci. 75, 387-390, (1986).

<29> Longenecker J.P., "NAZLIN-Transnasal Systemic Delivery of Insulin", in "Delivery Systems for Peptide Drugs", eds. Davis S.S:, Illum L., Tomlinson E., Plenum Press, (1987).

<30> Daugherty A.L., Liggit H.D., Mc Cabe J.G., Moore J.A., Patton J.S., "Absorption of recombinant Met-hGH from rat nasal mucose", Int. J. Pharm., 45, 197-206,(1988).

<31> Longenecker J.P., et al., "Effect of Na Taurodihydrofusidate on Nasal Absorption of Insulin in Sheep", J. Pharm. Sci., 76, 351-355,(1987).

<32> Illum L., et al., "Nasal Administration of Gentamicin Using a Novel Microsphere Delivery System", Int. J. Pharm., 46, 261-265,(1988).

<33> Davenport H.W., "Destruction of the Gastric Mucosal Barrier by Detergents and Urea", Gastroenterology, 54, 175-181,(1968).

<34> Davenport H.W., "Effect of Lysolecithin, Digitonin, and Phospholipase upon the Dog's Gastric Mucosal Barrier", Gastroenterology, 59, 505-509,(1970).

<35> Raehs S.C., et al., "Absorption Enhancement of Bacitracin upon Nasal Absorption of GHRH in Rats", in Proceeding of the 15th International Symposium on Controlled Release of Bioactive Materials, August 15-19,(1988), Basel.

<36> Sekine K., et al., "Pharmaceutical Powdery Compositions Containing Physiologically Active Polypeptides for Intranasal Administration", Jpn.

Kokai Tokkyo Koho JP 63,115,822 [88,115,822],(1986), (CA Vol.110, page 429, 1989).

<37> Kowarski H.R., "Pharmaceutical Composition and Method for Intranasal Administration", EPA 0285367,(1988).

<38> Yoshioka H., Fujita T., Goto A., "Effect of Glycyrrhizin on the phosphatidylcholine-Water System. ESR and Calorimetric Study", J. Colloid Interface Science, 133(2), 442-446,(1989).

<39> Japanese Kokai JP 63,010,735, published 10.01.1988.

<40> Ohwaki T., et al., "Effect of Dose, pH and Osmolarity on Nasal Absorption of Secretin in Rats. II. Histological Aspects of the Nasal Mucosa in Relation to the Absorption Variation due to the Effects of pH and Osmolarity", J. Pharm. Sci., 76 (9), 695-698,(1987).

<41> Illum L., et al., "Bioadhesive Microspheres as a Potential Nasal Drug Delivery System", Int. J. Pharm., 39, 189-199,(1987).

<42> Bjork E. and Edman P., "Degradable Starch Microspheres as a Nasal Delivery System for Insulin", Int. J. Pharm., 47, 233-238,(1988).

<43> Illum L., et al., "Microspheres as a Nasal Drug Delivery System", in Proceedings of the 15th

International Symposium on Controlled Delivery of Bioactive Material, August 15-19,(1988), Basel.

<44> Morimoto K., et al., "Enhancement of Nasal Absorption of Insulin and Calcitonin Using Polyacrylic Acid Gel", J. Pharm. Pharmacol., 37, 134-136,(1985).

<45> Pennington A.K., et al., "The influence of Solution Viscosity on Nasal Spray Deposition and Clearance", Int. J. Pharm., 43, 221-224,(1988).

<46> Hammami M., et al., "Expression of ACTH-Induced Corticosteroid Biosynthesis in Newborn Rat Adrenocortical Cells Cultured in Serum-Free and Carrier-Free Medium Containing a Cholesterol-α-Cyclodextrin Complex", Cel Biol. Toxicol., 2 (1), 41-52,(1986).

<47> Edgar H.P. and Sorensen A.R., "Nasal Formulations and a Process for Preparation therof", EPA# 87311054.8,(1987).

<48> Van de Donk H.J.M., et al., "The Effect of Preservatives on the ciliary Beat Frequency of Chicken Embryo Tracheas", Rhinology, 18, 119-133. 1980 42) Van de Donk H.J.M., et al., "The Influence of the pH and Osmotic Pressure upon Tracheal Ciliary Beat Frequency as Determinated with a New Photo-Electric Registration Device", Rhinology, 18, 93-104,(1980).

<49> Lee S.W., et al., "Nasal Sprays and Polyps", Nucl. Med. Commun., 5, 697-703,(1984).

<50> Buri I.P., "Hydrogels destinés à la muqueuse nasale. Controle physiologique", Pharm. Acta Helvetiae, 41, 88-101,(1966).

<51> Lee W.A. and Longenecker J.P., "Intranasal Delivery of Proteins and Peptides", BioPharm, APRIL, 30-37,(1988).