THE ADMINISTRATION OF DRUGS AND VACCINES BY THE INTRANASAL ROUTE

The nose is the outermost part of the respiratory tract and serves to warm, moisten and cleanse inspired air. With the exception of the olfactory area, it is lined by columnar ciliated epithelium with mucous glands and a rich sub-epithelial plexus of capillary blood vessels derived from the extensive bed of vascular erectile tissue covering the turbinate bones. A thin surface sheet of mucus, and any foreign adherent particulate matter, are propelled posteriorly towards the pharynx by the cilia. In normal subjects, nasal mucus flow rates measured by technetium 99 m tagging, average 5 mm/min and range from 0-20 mm/min (Proctor, Andersen & Lundqvist, 1973). Nasal secretion amounts to about a litre every 24 h moistening inspired air to 90% relative humidity (Proetz, 1959). Many local and systemic infections gain entry through the nose and various microorganisms can be isolated in a substantial proportion of asymptomatic subjects (Jacobson & Dick, 1941; Cooney, Hall & Fox, 1972). The nose is not, therefore, merely a passive conducting tube, its state alters with changes in temperature and atmospheric conditions and in response to infection. Clearly it is not an ideal route for consistent absorption of drugs or vaccines.

Three classes of medicinal products are applied by the nasal route; drugs for the alleviation of nasal symptoms; drugs which are inactivated in the gastrointestinal tract following oral administration and where the intranasal route is an alternative to injection, and vaccines.

In the control of nasal symptoms associated with infective, allergic or vasomotor rhinitis many drugs are used, including vasoconstrictors, antihistamines, corticosteroids and cromoglycate. Traditionally, therapeutic efficacy has been assessed subjectively by comparing the effects of test drug, placebo and sometimes a standard drug on symptoms of nasal obstruction, discharge and irritation. However, these assessments can now be supplemented by determinations of the surface temperature of the nasal mucosa (Biesalski & Marguardt, 1959) and by direct measurements of nasal airway resistance (Aschan & Drettner, 1964; Benson, 1971). Rebound vasodilation and nasal congestion is not uncommon following some vasoconstrictors and there are reports of iatrogenic chronic nasal obstruction which have improved when treatment was withdrawn (Maunsell, 1959).

Post-pituitary extract BPC administered as snuff or insufflation was formerly used to control polyuria in mild cases of diabetes insipidus. It is now largely replaced by lyspressin nasal spray since immunological pulmonary complications appear to be less following administration of the synthetic polypeptide (Pepys, Jenkins, Lachman & Mahon, 1966). The longer-acting desmopressin (1-des-amino-8-D-arginine vasopressin (DDAVP)) may also be given intranasally, 20 µg of DDAVP administered by this route being shown to be equivalent to approximately 2 µg administered by intravenous injection (Edwards, Kitau, Chard & Besser, 1973). Synthetic oxytocin may be given intranasally for milk let-down and to prevent engorgement in breast feeding although larger doses are required by the intranasal than by the parenteral route (Huntingford, 1961). It is not generally recommended in the induction of labour due to inconsistencies in nasal absorption. Oxytocin appears to be fairly free from local side effects when given intranasally but vasopressin may cause ulceration of the nasal mucosa, presumably due to its prolonged vasoconstrictor activity.

Avoidance of injection is also an attraction in the administration of vaccines since acceptability is increased, particularly in the young. Many vaccines have been administered intranasally but the most comprehensive series of studies has been carried out with the Wistar RA 27/3 strain live attenuated rubella vaccine and with inactivated and attenuated influenza vaccines. Higher titres of local nasal IgA antibodies are elicited by intranasal than by subcutaneous administration of the Wistar rubella vaccine although the circulating IgG antibody responses appear to be equivalent (Plotkin, Farquhar & Ogra, 1973; Al-Nakib, Best & Banatvala, 1975). Nasal antibodies should provide resistance at the portal of entry of infection and these greater nasal antibody titres have been correlated in volunteers with greater resistance to artificial challenge with partially attenuated Brown strain rubella virus (Ogra & Morag, 1975). Unfortunately, as with the posterior pituitary polypeptides, a greater dose of virus is needed to obtain an equivalent seroconversion or 'take' rate when live vaccine is administered intranasally (Zealley, Morrison & Freestone, 1974). In addition, seroconversion rates after intranasal

vaccination have been found to be influenced by the age of the vaccinees, the presence of nasal infection and the technique employed for vaccination (Puschak, Young, McKee & Plotkin, 1971; Hillary, 1971). It is clear that seroconversion rates greater than 95% are obtained less consistently following administration of vaccine by the intranasal than the subcutaneous route (Freestone, 1975).

Inactivated influenza vaccines also induce nasal IgA antibody responses when administered intranasally although the circulating antibody responses are poor in comparison with those elicited by parenteral administration of vaccine of an equivalent antigenic mass (Waldman, Jurgensen, Olsen, Ganguly & Johnson, 1973). There is evidence that vaccines administered by the intranasal route protect against infection but although they are well tolerated neither wet vaccine nor freeze-dried vaccine administered from metered dose aerosols have found great favour in the United Kingdom.

Live influenza vaccines are given by the intranasal route and have been shown to elicit greater nasal IgA responses and stimulate sturdier protection against challenge than equivalent standard inactivated saline influenza vaccines administered by injection (Beare, Hobson, Reed & Tyrrell, 1968; Downie, 1970; Freestone, Hamilton-Smith, Schild, Buckland, Chinn & Tyrrell, 1972). In most studies live vaccines have been administered as drops with patients lying flat on their backs on couches with their heads hyperextended (Beare, 1975). This technique is ill suited to mass vaccination or for the vaccination of elderly subjects who are, of course, at particular risk from infection. White, Freestone, Bowker, Barnes, Letley & Ferris (1975) showed that higher seroconversion rates were obtained following the administration of live WRL 105 strain influenza vaccine as nose drops employing the technique described above than were obtained with any one of three spray devices. However, the seroconversion rate obtained with vaccine given by one particular device, the Jencon-Repette syringe with disposable Risdon nasal applicators, was almost as good as that which followed the administration of vaccine as drops. These investigators did not find any correlation between seroconversion rates and mean droplet sizes of sprayed vaccine which ranged from 70 to 400 μ . Devices which discharged vaccine in small droplet sizes were not included in this study since changes in pulmonary function have been described following natural influenza and following the administration of other live influenza vaccines (Leeder, Gill & Peat, 1974; Rosenweig, Dwyer, Ferstenfeld and Rytel, 1975) and it seemed undesirable to deliver vaccine in droplets

of less than 5 to 10 μ which might be carried into the lower respiratory tract. Furthermore risk of inadvertent vaccination was thought to be greater with fine droplet aerosols. Aoki & Crawley (1976) set out to investigate techniques and dose schedules for nasally applied antiviral drugs and vaccines. In their paper in this issue of the journal (page 869) they report a comparison of the deposition and clearance of various concentrations and volumes of aqueous solutions of human serum albumin radiolabelled with technetium 99 m administered intranasally either as drops to recumbent volunteers, or by the Jencon-Risdon device to seated volunteers. In contrast with the results of White *et al.* (1975) good distributions of technetium in the nasal cavity with little spread below the plane of the hard palate were obtained in 62 (85%) of 73 drop applications and 1 (4%) of 27 spray applications. The mean rate of removal of intranasal technetium from the nose ($T_{\frac{1}{2}}$) varied both within and between volunteers and ranged overall from 5 to 90 minutes irrespective of the method of application.

Three mechanisms, impaction, sedimentation and diffusion, have been described for the deposition of particles in the respiratory tract (Stuart, 1973). Impaction deposition occurs when an airway is suddenly deflected, for example by turbinates, and it occurs because the inertia of an airborne particle causes it to travel in its initial path. Thus impaction deposition is related to particle size, the velocity of the airstream and the angle of bend in the airway. Impaction deposition is the principal method for deposition of large particles ranging from a few to 200 μ most of which are deposited in the nose. In a system in which bromine-82 radiolabelled polystyrene particles of 1 to 10 μ were drawn through the nose and mouth of breath-holding subjects, Hounam, Black & Walsh (1970) found that nasopharyngeal deposition indices correlated with particle size, and rather better with nose-mouth pressure differences than with flow rates. However, in the intranasal administration of live vaccine a point of concern is that Goodlow & Lennard (1961) in studying aerosols of *Pasteurella tularensis* in guinea-pigs and rhesus monkeys and Druett, Henderson, Packman & Peacock (1953) in studying anthrax in rhesus monkeys all showed that more cells were required to produce infection when they were delivered in large particles. In addition, Buckland, Bynoe & Tyrrell (1965) showed in volunteers that infection with Cocksackie A21 was more readily achieved when the virus was placed anteriorly in the nose.

In the treatment of nasal symptoms the patient is able to adjust the dose and frequency of dosage. In these circumstances it is perhaps less important

that drugs are delivered in formulations and by techniques that are optimal. Thus there are a multiplicity of methods for administration of drugs for the alleviation of nasal symptoms; for example, vasoconstrictors and corticosteroids have been given as insufflations, nasal drops, nasal sprays from plastic squeeze bottles, and latterly from metered dose aerosols. Mirimanoff (1969) studied the effects of tonicity, pH and viscosity of solutions of salt and glucose on ciliary activity in guinea-pigs and human subjects but few other formal comparative studies on the effects of formulation, of the devices used and the techniques of application have been reported.

Three groups of factors seem likely to affect the efficacy of drugs or vaccines administered by the nasal route.

The physiological condition of the nose-vascularity, speed of mucus flow, presence of

infection and the prevalent atmospheric conditions; the nature of the materials administered—volume, concentration, density, viscosity, pH, tonicity, and any pharmacological or immunological activity of the active principles or excipients; the techniques and devices used for administration—droplet size, site of deposition, percentage lost into gastrointestinal or lower respiratory tracts and anteriorly from the nose, and the time course of the material's removal. Further studies of the relative importance of these factors seems justified, particularly if more trials of nasally acting antiviral drugs and vaccines are contemplated.

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