Decreases in Ciliary Beat Frequency Due to Intranasal Administration of Propranolol

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Abstract □ Recently the intranasal application of 5% propranolol was proposed in order to prevent the extensive first-pass metabolism of this drug. The ciliary epithelium in the nose affects the removal of dust, allergens, and microorganisms. The decreasing effect of propranolol on the ciliary beat frequency of human adenoid tissue and chicken embryo tracheas was measured with a photoelectric registration device. After nasal application of 5% propranolol, the drop is diluted by the nasal mucus. It was found that even 0.1% propranolol had a deleterious effect on the cilia of chicken and human tissue. Ciliary movement was arrested irreversibly within 20 min.

Keyphrases □ Propranolol—decrease in ciliary beat frequency due to intranasal administration □ Intranasal administration—propranolol, decrease in ciliary beat frequency □ Ciliary movement—decrease due to intranasal administration of propranolol

The extensive use of nasal drops necessitated the investigation of the effects of nasal medication on the ciliary beat frequency. The nasal ciliary epithelium effects the removal of dust, allergens, and microorganisms that are precipitated after inhalation. This nasal clearance is a physiological defense mechanism which should not be disturbed. A method has been developed to investigate the influence of drugs on the ciliary beat frequency (1). With this method the ciliary beat frequency of chicken embryo tracheas is measured with a photoelectric registration device. The effects of preservatives (2) and nasal drops (3) have been investigated previously. A good correlation has been found between the ciliary beat frequency of ciliary epithelium of human adenoids and of chicken embryo tracheas (4). Recently, the intranasal application of propranolol has been suggested in order to prevent the first-pass effect of this drug after oral administration (5). As propranolol is used in chronic therapies, the effects of intranasal application on the ciliary beat frequency may be important. Therefore, the effect of propranolol on the ciliary beat frequency of chicken embryo tracheas and human adenoid tissue was investigated.

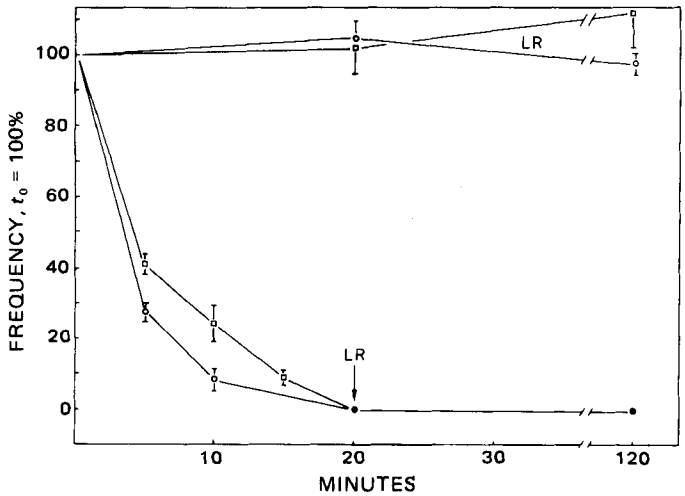

Figure 1—*Time* versus *ciliary beat frequency plot: effect of 0.1% propranolol hydrochloride on the cilia of human adenoids and chicken embryo tracheas. Locke-Ringer (LR) solution was used as a reference. Key: (□), human; (○), chicken; (●), Locke-Ringer.*

Table I—The Decreasing Effect of Propranolol on the Ciliary Beat Frequency of Chicken Embryo Tracheal Epithelium and Human Adenoid Epithelium

Compound	Frequency[a], % Time 2 min	10 min	20 min	Species
Propranolol hydrochloride, 1%	0	0	0	Chicken
Propranolol hydrochloride, 0.1%	70	8	0	Chicken
Propranolol hydrochloride, 0.1%	77	25	0	Human

[a] Frequency as a percentage of the initial frequency.

EXPERIMENTAL

The effects of a solution containing 1% propranolol hydrochloride[1], made isotonic with sodium chloride and of a 10-fold dilution of this solution in Locke-Ringer, were investigated. Both solutions were adjusted to pH 7.4. The effects on the ciliary beat frequency were assessed on six different tracheas for each concentration and for the reference (Locke-Ringer) and on pieces of six different human adenoids for the 10-fold dilution and the reference.

RESULTS

The effects of 1 and 0.1% propranolol are demonstrated in Table I. Frequencies are listed as a percentage of the frequency just before the start of the experiments. The solution containing 1% propranolol arrested ciliary movement of chicken embryo tracheas within 2 min. The 10-fold dilution arrested the ciliary movement of both human adenoids and chicken embryo tracheas within 20 min. This effect was irreversible: rinsing with Locke-Ringer solution after a 20-min contact with 0.1% propranolol did not restore ciliary movement within 2 hr.

The effects of 0.1% propranolol are shown in more detail in Fig. 1 with *SEM* values indicated by vertical bars.

DISCUSSION

The use of a nasal drop containing 5% propranolol has been suggested (5). This nasal drop is diluted by the nasal mucus after application, therefore, the investigation began with 1% propranolol which had a deleterious effect on ciliary movement of chicken embryo tracheas. Propranolol (0.1%) also irreversibly arrested the ciliary movement of chicken and human cilia within 20 min. It is not likely that the nasal drop will be diluted more than 50 times in 20 min, especially since it interferes with the nasal clearance.

For repeated intranasal administration of propranolol, its ciliotoxicity should be taken into account.

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[1] Propranolol hydrochloride (B.P.) 0504001/4 PO 821A ICI

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(5) A. Hussain, T. Foster, S. Hirai, T. Kashihara, R. Batenhorst, and M. Jones, *J. Pharm. Sci.*, **69**, 1240 (1980).

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Influence of Ethylene Oxide Exposure on the Extraction of Indomethacin from Dimethicone Polymeric Rods

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ABSTRACT □ Dimethicone polymeric rods were made to contain 0.3, 2.0, or 3.3% by weight of indomethacin. For each different loading of indomethacin, some of the rods were treated with ethylene oxide at 55° for 1 hr, while others were not exposed to the gas. Treated and untreated rods were sliced, placed in ethanol to extract the indomethacin, and the concentrations of indomethacin in the extracts determined by fluorometry and high-performance liquid chromatography (HPLC). After ethylene oxide treatment, the quantity of indomethacin in the extracts was significantly reduced in rods containing 0.3 and 2.0% indomethacin. For the rods containing 3.3% indomethacin, the recovery of the drug from treated rods was not significantly different from those not exposed.

Keyphrases □ Ethylene oxide—extraction of indomethacin from dimethicone polymeric rods □ Indomethacin—dimethicone polymeric rods, influence of ethylene oxide exposure □ Polymeric rods—dimethicone, ethylene oxide exposure on extraction of indomethacin □ Fluorometry—determination of influence of ethylene oxide exposure on the extraction of indomethacin from dimethicone polymeric rods □ High-performance liquid chromatography—determination of influence of ethylene oxide exposure on the extraction of indomethacin from dimethicone polymer rods

The development of simple systems or devices for drug delivery over extended periods has potentially wide usage, especially for delivery of compounds to selected sites in the body. In this regard, experiments have been performed with a system which can provide a sustained release of nonsteroidal anti-inflammatory drugs such as indomethacin or naproxen from dimethicone polymeric rods (1). In these and other studies (2, 3) the quantity of drug released *in vivo* is determined by measuring the residual amount of drug in the rods at various time periods and subtracting it from values from similar rods prepared in an identical manner but which were not placed in the body. The measurements are performed on ethanolic or methanolic extracts of the rods.

Before being fitted into the body, such rods must be sterilized. Since autoclaving and chemical methods (such as placing in aqueous ethanol) appear unsuitable for this system, ethylene oxide gas treatment has been used.

The present study indicates that by using this method of sterilization, there is a decrease in the percentage of indomethacin that can be extracted into ethanol from rods containing the drug at low concentrations (<3% w/w).

EXPERIMENTAL

Indomethacin[1] was recrystallized, dried, and either 0, 10, 60, or 100 mg was thoroughly mixed with 3 g of dimethicone[2]. Following the addition of catalyst (15 mg) the different mixtures were forced into vinyl tubing (french gauge 5, 1-mm i.d.)[3] and allowed to polymerize. Rods of 1-cm length were cut and weighed and either stored at room temperature or subjected to ethylene oxide exposure (1.2–1.4 g/liter) in a stainless steel sterilizer[4]. In this apparatus the gas was released from ampuls into a chamber initially evacuated to 150 mm Hg. Following exposure to the gas for 1 hr at 55°, the rods were aerated for at least 12 hr and left for 2 days at room temperature.

Rods containing indomethacin were weighed, cut into thin slices, and the drug extracted with ethanol (2 ml/day for 4 days). The amounts of indomethacin in the extracts were determined by fluorometry and HPLC with standard solutions of indomethacin prepared from the recrystallized compound. For the fluorometric analysis, samples were assayed in duplicate using a spectrophotofluorometer[5] with an excitation wavelength of 295 nm and an emission wavelength of 361 nm. Continuous scan recordings over an emission range of 300 to 450 nm (constant excitation wavelength of 295 nm) were also made of certain extracts of the gassed and nongassed rods. For HPLC, 10 μl samples were injected into a C18 μ Bondapak column[6] with a mobile phase of methanol–50 m*M* KH_2PO_4 (3:1), pH 6.72, and a flow rate of 2 ml/min. The UV absorbance at 230 nm of the column eluate was continuously recorded with a variable wavelength UV detector[6]. Heights of the peaks corresponding in position to the indomethacin standards were measured to determine the amounts of indomethacin in the extracts. These amounts, compared with those determined to be present initially on the basis of the quantity of indomethacin in the mixture and the weight of each rod, were used to calculate percentage recoveries.

RESULTS

For the rods not subjected to ethylene oxide exposure, over 90% of the incorporated indomethacin was recovered into ethanol when measurements on the extracts were made by fluorometry (Fig. 1). This was confirmed by HPLC of the extracts of rods made from the 60 and 100 mg/mixture. (The HPLC system used did not allow a reliable measurement of indomethacin in the extracts obtained from the 10 mg/mixture rods as the peaks assigned to indomethacin were not sufficiently large to be accurately quantitated.) Following ethylene oxide treatment, however, the recovery of indomethacin into alcohol was significantly reduced for

[1] Sigma Chemical Co., St. Louis, Mo.
[2] Silastic, 382 medical grade elastomer, Dow Corning Corp., Midland, Mich.
[3] Latex Products Pty.
[4] Victoria MK II, Medical Electronics Ltd, U.K.
[5] Aminco-Bowman, Model 768 G, American Instrument Co., Silver Spring, Md.
[6] Waters Associates, Milford, Mass.

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