TRANSTYMPANIC IONTOPHORESIS OF N-ACETYL-CYSTEINE

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This paper reports the results of experiments carried out on guinea pigs showing that iontophoresis can further the passage of N-acetyl-cysteine, a well known mucolytic agent, through the tympanic membrane. Iontophoresis of N-acetyl-cysteine may be of some usefulness in the treatment of those cases of otitis media which produce a typical viscous secretion (glue ear). The mucolytic properties of cysteine depend mainly on its free -SH group, which breaks the disulfide bridges of the mucoproteins thus giving rise to a reduction of the viscosity of the secretion (Uhde G.E., I957; Kun E., I96I; Echols D.F. et al., I975).

N-acetyl-cysteine, having the amino group acetylated, behaves as a weak acid and dissociates as an anion even in weak alkaline solutions. It seemed interesting to check if by means of iontophoresis N-acetyl-cysteine instilled in the external auditory canal moving towards the anode could pass through the tympanic membrane and reach the middle ear.

MATERIALS AND METHODS

N-acetyl-cysteine was a commercial product (Merck, Darmstadt, West Germany). It was dissolved in 0.I M phosphate buffer pH 7.2 immediately before use, at a concentration of 0.I65 or 0.33%.

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A iontophoretic apparatus (Model 22 Medical System Ltd., Baton Rouge, Louisiana, U.S.A.) was used, equipped with a milli-amperometer. The catode consisted of a needle of inert electric material fixed in an isolated base; the anode was a small electric wire loop.

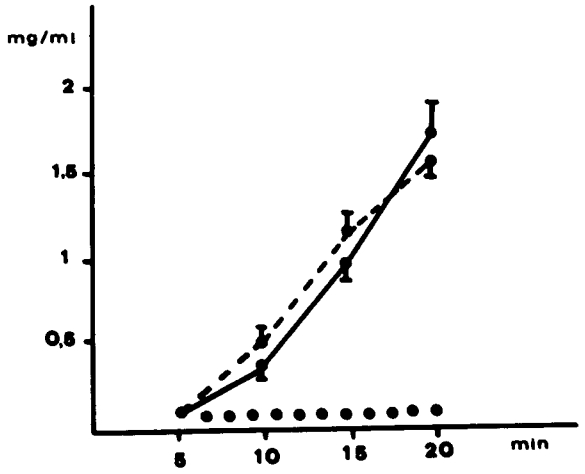
The eeperiments were made on guinea pigs, under narcosis obtained by intraperitoneal injection of sodium thiopental (I5 mg/Kg). After incision of the tissues behind the ear, the bulla (which in humans corrisponds to the middle ear) was perforated by a needle and injected with 0.I ml of 0.I M phosphate buffer pH 7.2. The external auditory canal was filled with the solution of N-acetyl-cysteine (0,2 ml), taking care to prevent the formation of air bubbles. The integrity of the tympanic membrane was always checked by otoscopic examination. The catode was placed in the external auditory canal so that it was in contact with the solution of N-acetyl-cysteine without touching the walls of the canal. The anode was applied to the wall of the temporal bone by means of a conductive paste. The iontophoresis was carried out at an intensity of 0.7 mA for 5,I0,I5 or 20 minutes, and then the solution injected in the middle ear was aspired and the cavity washed with 0.I ml phosphate buffer. The pooled solution and washing were added with 0.I ml I N HCI in order to prevent the possible autoxidation of N-acetyl-cysteine.

The amount of N-acetyl-cysteine in the solution taken off from the middle ear was estimated by determining spectrophotometrically the reduction of 5,5' - dithiobis-2-nitrobenzoic acid (Ellman G.I., I959).

Experiments were carried out on 24 animals (48 ears); other 4 animals were used as controls in which no current was applied after having filled the middle ear and the external auditory canal with buffer and N-acetyl-cysteine solution respectively.

RESULTS

Fig. I shows the concentration of N-acetyl-cysteine found in the endotympanic specimens of the experimental and control groups, in relation to the length of the iontophoresis and to the concentration of N-acetyl-cysteine solution in the external auditory canal.



LEGEND TO FIGURE I

Endotympanic levels of N-acetyl-cysteine (± sem) in the course of transtympanic iontophoresis.

_____: concentration in the external auditory canal -0,I6%

- - - - - -: concentration in the external auditory canal -0,33%

.....: control group

It is evident that after iontophoresis significative amounts of N-acetyl-cysteine were detected in the middle ear. The controls however were absolutely negative. Thus it was

demonstrated that N-acetyl-cysteine can pass across the tympanic membrane under the influence of an electric field. Furthermore, the amount of N-acetyl-cysteine which passed through the tympanic membrane showed, as expected, an almost linear dependence on the duration of iontophoresis. On the contrary, the increase in the concentration of the N-acetyl-cysteine solution in the external auditory canal did not increase the amount of it that passed through the membrane. This latter result seems to indicate that the limit of permeability of the membrane, which is represented by the possible sites through which the molecules of N-acetyl-cysteine can pass (Lim D.I.,I968), is quite low and thus even low concentrations of the solution are sufficient to allow it to cross the membrane by iontophoresis.

On the whole, the results obtained with guinea pigs suggest that transtympanic iontophoresis of N-acetyl-cysteine may be a useful tool in the treatment of secretory otitis media, in particular for the reduction of the high viscosity of the mucus, which causes glue ear and is responsible for the permanence of otitis media.

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