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In vitro ciliotoxicity of propranolol isomers

G.S.M.J.E. Duchateau [1], J. Zuidema [1], W.A.J.J. Hermens [2] and F.W.H.M. Merkus[1,2]

[1] *Department of Biopharmaceutics, University of Amsterdam 1018 TV Amsterdam and* [2] *Center for Bio-Pharmaceutical Sciences, Leiden University, 2300 RA Leiden (The Netherlands)*

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It has been reported that the β-adrenoceptor blocking agent, propranolol, is absorbed rapidly and completely from the nasal mucosa after intranasal administration in humans (Hussain et al., 1980). The feasibility of this repeated intranasal propranolol administration is, however, limited, because propranolol is extremely ciliotoxic. When ciliotoxicity of propranolol was tested in vitro at a concentration 50 times less than the concentration used in the nasal formulation, ciliary movement was arrested within 20 min (Van de Donk and Merkus, 1982). As ciliary activity is the most important factor in the mucociliary clearance it must not be hampered.

This toxic effect of propranolol was also found with other cilia-like structures, such as the flagella of human spermatozoae. The influence on sperm mobility is caused by the membrane-stabilizing effect of the drug (Peterson and Freund, 1975). Propranolol has been proposed as a vaginal contraceptive agent (Zipper et al., 1983). After oral administration (80 mg), however, the propranolol concentration in seminal plasma is much lower than the in vitro concentration necessary to reduce the sperm mobility by 50% (Mahajan et al., 1984).

A significant reduction in mucociliary clearance was reported after oral administration of propranolol (Dorow et al., 1984). Twenty-four patients receiving 2 × 40 mg propranolol daily had a significantly reduced mucociliary clearance compared with placebo treatment. A reduction in ciliary beat frequency (CBF) via an inhibition of β-adrenoceptors in the ciliated epithelium was suggested by the investigators.

Recently, Lopez-Vidriero et al. (1985) described the in vitro stimulation of CBF with the β-sympathicomimetic drug isoprenaline. The racemic mixture of isoprenaline increased the CBF of rat tracheal explants to 150% of the initial frequency at a concentration of 10^{-3} mol/l. The dextro-isomer of isoprenaline, which has a very low potency on β-sympathicomimetic receptors, had no effect on CBF. The increase in CBF caused by the racemic mixture could be completely inhibited with propranolol at a concentration of 10^{-7} mol/l. They concluded that stimulation of CBF by laevo-isoprenaline is mediated by β-adrenoceptors. It is therefore important to determine whether the ciliotoxic effect of propranolol, reported by Van de Donk and Merkus (1982), is mediated by β-adrenoceptor blockade or by a membrane-stabilizing effect.

We studied with our in vitro model (Van de Donk et al., 1980) the ciliotoxicity of both propranolol isomers in a concentration range from $0.6–8 \times 10^{-3}$ mol/l. Isotonic solutions of the iso-

Correspondence: F.W.H.M. Merkus, Center for Bio-Pharmaceutical Sciences, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands.

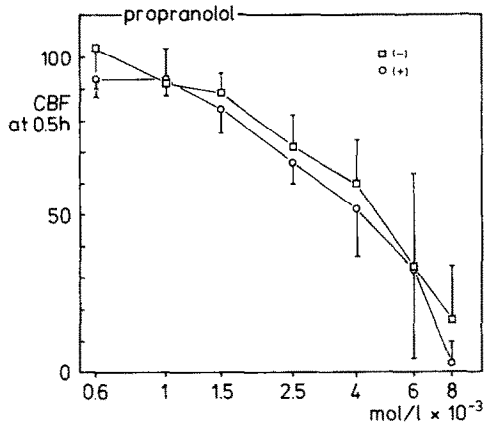

Fig. 1. Plot of the reduction in ciliary activity of chicken tracheal tissue after incubation for 30 min in isotonic solutions of (+) and (−)-propranolol. Results are presented as the mean ± S.D. (n = 6), initial frequency = 100%. □ = (−)-propranolol: ○ = (+)-propranolol.

mers were made in Locke-Ringer solution (pH = 7.4). Ciliary activity of chicken ciliated embryonal tissue was studied before (= 100%), and after 30 min incubation of the tissue in the isomer solutions. Each concentration and isomer was tested 6 times. The decrease in ciliary activity was plotted versus the log-concentration. The results are presented in Fig. 1.

The found differences in CBF reduction caused by the propranolol isomers were tested with a Student *t*-test for paired results. The differences in CBF reduction caused by the propranolol isomers were non-significant at all the tested concentrations ($P > 0.1$).

From our study two conclusions can be drawn. In our experiments a 50% reduction of CBF is achieved at a propranolol concentration of approximately 4×10^{-3} mol/l. This is much higher than the normal therapeutic serum or plasma concentration ($\approx 0.1-0.4 \times 10^{-6}$ mol/l). The reduction on mucociliary clearance by propranolol as found by Dorow et al. (1984) in patients, is therefore not likely to be due to ciliary inhibition. However, it cannot be excluded that propranolol exhibits a ciliotoxic effect in this concentration range on the condition that also a β-adrenoceptor agonist is present as is possible in the in vivo situation.

Secondly, we found in our experiments no difference in ciliotoxicity between the two isomers. Both isomers of propranolol exhibit different biological properties, especially the difference in β-adrenoceptor blockade are large. The dextro-isomer of propranolol (+) has less than one-hundredth of the potency of the laevo-isomer (−) in blocking β-adrenoceptors. Their membrane-stabilizing activities, however, are equal. It can therefore be concluded that the membrane-stabilizing effect is the best explanation for the in vitro ciliotoxic effect of propranolol.

References

Dorow, P., Weiss, Th., Felix, R. and Schmutzler, H., The influence of propranolol, metoprolol, and mepindolol on mucociliary clearance in coronary heart disease patients without pulmonary disease. Int. J. Clin. Pharm. Ter. Tox., 22 (1984) 108–111.

Hussain, A., Foster, T., Hirai, S., Kashihara, T., Batenhorst, R. and Jones, M., Nasal absorption of propranolol in humans. J. Pharm. Sci., 69 (1980) 1240.

Lopez-Vidriero, M.T., Jacobs, M. and Clarke, S.W., The effect of isoprenaline on the ciliary activity of an in vitro preparation of rat trachea. Eur. J. Pharmacol., 112 (1985) 429–432.

Mahajan, P., Grech, E.D., Pearson, R.M. Ridgway, E.J. and Turner, P., Propranolol concentrations in blood serum, seminal plasma and saliva after a single oral dose. Br. J. Clin. Pharmacol., 18 (1984) 849–852.

Peterson, R.N. and Freund, M., The inhibition of the motility of human spermatozoa by various pharmacological agents. Biol. Reprod., 13 (1975) 552–556.

Van de Donk, H.J.M., Zuidema, J. and Merkus, F.W.H.M., The influence of the pH and osmotic pressure upon tracheal ciliary beat frequency as determined with a new photoelectric registration device. Rhinology, 18 (1980) 93–104.

Van de Donk, H.J.M. and Merkus, F.W.H.M., Decreases in ciliary beat frequency due to the intranasal administration of propranolol, J. Pharm. Sci., 71 (1982) 595–596.

Zipper, J., Wheeler, R.G., Potts, D.M. and Rivera, M., Propranolol as a novel, effective spermicide: preliminary findings. Br. Med. J., 287 (1983) 1245–1246.