Pharmacological Spectrum of Metipranolol 
and Experience in Clinical Use

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With 6 Figures

Introduction

In the past few years $\beta$-receptor blockers have assumed a firm although not entirely undisputed position in the treatment of glaucomas. This indication came quite unexpectedly. When the ocular pressure of glaucoma patients who were receiving oral treatment with $\beta$-receptor blocking agents for other diseases, e. g. angina pectoris or hypertension, was measured a pressure reducing, i. e. therapeutic effect, was revealed [1, 2].

In 1899 Jonnesco published a paper entitled "Die Resektion des Halssympathikus in der Behandlung des Glaukoms" [3]. This early paper thus provided indications of an influence of the autonomic nervous system on intraocular pressure.

Although there does not exist any doubt nowadays that $\beta$-receptor blocking agents are able to reduce increased intraocular pressure, the mechanism of this therapeutic effect has — as far as we know — not been absolutely clarified, all the more so as both $\beta$-blocking agents and adrenergic stimulants (for example noradrenaline, dopamine, phenylephrine) can reduce elevated ocular pressure [4, 5]. Whereas it was originally assumed that the ocular pressure reducing property of $\beta$-blocking agents is related directly to a local anaesthetic or membrane-stabilizing property [6], we now know that this assumption is incorrect as substances without any local anaesthetic quality worth mentioning e. g. timolol (the following always refers to S-timolol) and metipranolol, reduce ocular pressure.
Furthermore it has been seen that too pronounced an anaesthetic quality is not only unnecessary but also limits tolerance. This is probably also the reason why $\beta$-blocking agents with an excessive anaesthetic quality are not used in the therapy of glaucoma.

**Pharmacological Characterization of Metipranolol**

$\beta$-receptor blockers, which are competitive antagonists may be characterized as follows:

1. Affinity to $\beta$-receptor, i.e. tendency to bind themselves to the receptor;
2. selectivity, i.e. the preferred antagonistic action on $\beta_1$ (cardiac) or $\beta_2$ (smooth-muscular, i.e. bronchial and vasal) receptors;
3. their intrinsic sympathomimetic action and
4. the membrane-stabilizing or surface-anaesthetic quality. The surface-anaesthetic property is undoubtedly of significance for the suitability of a $\beta$-blocker as a glaucoma treatment.

To be able to classify metipranolol in the spectrum of $\beta$-blocking agents you will find some physico-chemical characteristics along with the chemical structure in Table 1. In ophthalmological use the liposolubility (expressed as octanol/water quotient) should be of vital significance as an extremely hydrophilic or extremely lipophilic substance probably does not penetrate the various tissue layers so well as a $\beta$-blocker which is both hydrophilic and lipophilic. As can also be seen in Table 1, there are no relevant differences between the various $\beta$-blockers under discussion as far as their elimination kinetics are concerned [7—15]. It is questionable whether the differences in protein binding (between 10 and 93%) are of significance for topical application.

**$\beta$-blocking Potency**

It is possible to demonstrate the $\beta$-blockade and its potency in a wide variety of systems (isolated cells, isolated organs, anaesthetized or conscious animals and in humans).

The antagonism to the effect of the $\beta$-stimulant isoprenaline is by definition very suitable for characterization (see Bartsch et al., 1977 [16], for details on the method). The results illustrated in Fig. 1 show only relatively slight differences with regard to potency,