# Effects of trimetaquinol on equine pulmonary vascular and airway smooth muscle*

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Trimetaquinol [TMQ: 1-(3′,4′,5′-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride] a potential β-sympathomimetic bronchodilator (Iwasawa & Kiyomoto 1967), has been shown to be an effective tracheal smooth muscle relaxant in guinea-pigs (Iwasawa & Kiyomoto 1967; Brittain 1972; Brittain et al 1970, 1976) and an inhibitor of experimental bronchospasm in guinea-pigs and cats (Brittain et al 1970; Brittain 1972). In addition, clinical studies with TMQ indicated that the drug was an effective bronchodilator in mild to moderate asthma (Yamamura & Kishimoto 1968). It may be of value to determine the in vitro effects of bronchodilators on pulmonary vascular smooth muscle as well as airways (Hanna & Eyre 1979), since it is possible that, in vivo, inhaled bronchodilators may be distributed to the pulmonary vasculature, altering the vessel smooth muscle tone and consequently the pulmonary blood flow. This consideration plus the fact that TMQ has a non-selective β-adrenergic action and some papaverine-like characteristics (Sato et al 1967; Brittain 1972; Brittain et al 1970, 1976) prompted these preliminary investigations of the action of TMQ on an integrated airway and a pulmonary vascular smooth muscle system from horse. Tissues from horse lung were employed because of the size of the pulmonary system, and the reported similarity of equine and human lung at the subgross and gross anatomical levels (McLaughlin et al 1961; Tyler et al 1971).

Pulmonary venous and tracheal smooth muscle was obtained from normal horses freshly killed in a local abattoir. Tissues were prepared according to the methods previously outlined (Hanna & Eyre 1978, 1979) and suspended in 10 and 20 ml organ baths with Krebs-Henseleit solution aerated with 95% $O_2$/5% $CO_2$ at 37 °C. The relaxant effects of TMQ were measured (isotonically) by first contracting the vein with an ED50 concentration of histamine ($8{\cdot}0 \times 10^{-7}$ M) and then adding increasing concentrations of TMQ in a cumulative fashion after the contractile response had reached maximum. Relaxation responses were expressed as percent inhibition of the histamine ED50 contraction. For tracheal studies, the relaxant effects of TMQ were measured (isometrically) by first pre-incubating the tissues with single concentrations of TMQ for 6 min, then challenging the tissues with an ED50 concentration of carbachol ($5{\cdot}0 \times 10^{-7}$ M). The relaxant effects of TMQ on trachea were expressed as percent inhibition of the carbachol response. Standard statistical procedures were employed to calculate means, standard error (s.e.m.) and Student's *t*-test values. The following drugs were used: histamine dihydrogen chloride (Fisher Scientific Co.) and carbamyl choline chloride (Aldrich Chemical Co.). Trimetaquinol was a generous gift from Warner-Chilcott Laboratories.

TMQ consistently and effectively relaxed strips of equine tracheal smooth muscle contracted to carbachol. The effective dose range was broad ($10^{-9}$ to $10^{-3}$ M) and under the given experimental conditions, TMQ did not produce 100 per cent inhibition of the carbachol ED50 response (Fig. 1). In contradistinction, TMQ exhibited a dual response on the histamine-contracted pulmonary vein. Strips of venous smooth muscle first relaxed then, with increasing TMQ concentrations, the tissues contracted. The upper and middle tracings in Fig. 2 show clearly the effects of TMQ on histamine contracted and non-contracted tissues. It is also evident that tissues responded with different degrees of relaxation and contraction to TMQ. The complete dose-response curve is given in Fig. 1 and shows that TMQ produced approximately 50 per cent inhibition of histamine contractions up to concentrations of $10^{-7}$ after which higher concentrations produced contractions. TMQ when given

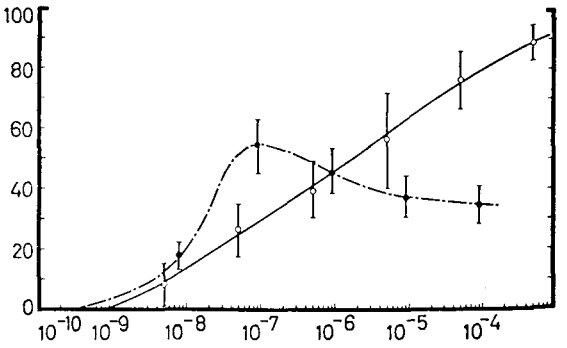


FIG. 1. Effects of trimetaquinol (TMQ) on histamine-contracted, equine pulmonary vein (n = 6) ●——● and carbachol-contracted, equine tracheal smooth muscle (n = 4) ○——○. Abscissa: log molar concentration of TMQ. Left ordinate: percent inhibition of the histamine ED50 ($8{\cdot}0 \times 10^{-7}$ M) response on the pulmonary vein by TMQ. Right ordinate: percent inhibition of the carbachol ED50 ($5{\cdot}0 \times 10^{-7}$ M) response on the trachea by TMQ.

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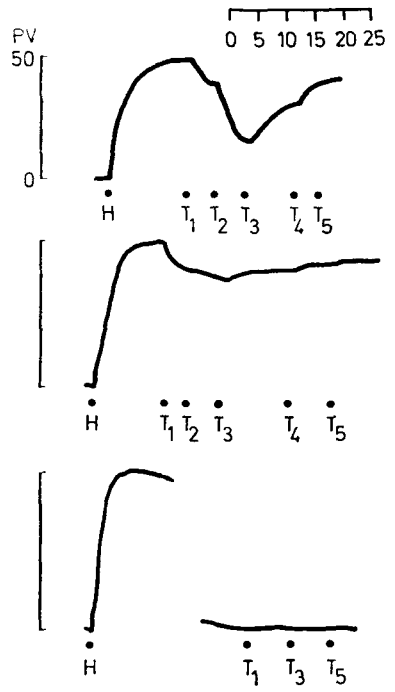


FIG. 2. Tracings of polygraph recordings illustrating the effects of cumulative additions of trimetaquinol on histamine ED50-contracted (upper and middle tracings) and uncontracted (lower tracing) equine pulmonary vein. Drug concentrations are as follows: histamine (H): $8{\cdot}0 \times 10^{-7}$ trimetaquinol (T): $T_1$: $8 \times 10^{-9}$; $T_2$: $9 \times 10^{-8}$; $T_3$: $9 \times 10^{-7}$; $T_4$: $9 \times 10^{-6}$; $T_5$: $9 \times 10^{-5}$ M. Time is given in 5 min intervals.

alone did not produce contractions even at final bath concentrations of approximately $10^{-4}$ M (Fig. 2: lower tracing).

The present results demonstrate that TMQ is an effective relaxant of horse trachea contracted to carbachol and are in agreement with studies on guinea-pig trachea (Brittain 1972; Brittain et al 1970). Compared with the effects of the $\beta_2$-sympathomimetic bronchodilators, salbutamol and terbutaline, on horse trachea (Hanna & Eyre 1979) TMQ was effective at lower threshold doses but had a less specific action as suggested by a broader dose-response curve. Like salbutamol and terbutaline, TMQ antagonized carbachol contractions incompletely, although very high concentrations of drug may have abolished the carbachol response.

It has been suggested that TMQ may have two modes of action on airways (Iwasawa & Kiyomoto 1967; Brittain et al 1970). At low concentrations the drug action may be primarily on the $\beta$-adrenoceptor whereas, at high concentrations TMQ may act as a cyclic nucleotide phosphodiesterase inhibitor due to a papaverine-like molecular character. Thus the broad dose-response curve may actually be composed of two overlapping curves, although this hypothesis has yet to be clearly established. TMQ produced two effects on horse pulmonary vein: an initial potent relaxation followed by contraction. In a previous investigation (Hanna & Eyre 1979), the specific $\beta_2$-adrenoceptor stimulants, salbutamol and terbutaline only relaxed horse pulmonary vein that had been contracted by histamine (ED50). TMQ may act like the $\beta$-sympathomimetic, isoprenaline, which has been shown to first relax then, at high concentrations, stimulate isolated human (Houghton & Phillips 1973) and canine (Joiner et al 1973) pulmonary venous smooth muscle. The TMQ contractile effects may be mediated, like isoprenaline, by the $\alpha$-adrenoceptor (Joiner et al 1973). However, the evidence that equine pulmonary vein responds with contractions to phenylephrine (Hanna & Eyre 1978), but does not contract to TMQ alone, contradicts this suggestion. Further studies are required to explain adequately the in vitro actions of this drug on the airways and pulmonary vasculature of horse. We conclude that the effects of trimetaquinol in the lung are not limited to airway smooth muscle and that this drug may not be a specific $\beta$-adrenoceptor stimulant.

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