STUDIES ON TETRAHYDROISOQUINOLINES (THI) (VIII) PHARMACOLOGICAL PROPERTIES OF METABOLITES OF A NEW ADRENERGIC β-STIMULANT, TRIMETOQUINOL

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A new adrenergic β-stimulant, l-1-(3, 4, 5-trimethoxybenzyl)-6, 7-dihydroxy-1, 2, 3, 4-tetrahydroisoquinoline HCl (trimetoquinol), exhibits strong bronchodilator effect as well as hypotensive, positive inotropic and chronotropic actions (1-7). Recently, the metabolic fate of this compound was studied in detail and it was found that part of trimetoquinol (TMQ) was O-methylated to form both 6- and 7-methoxytrimetoquinol (6- and 7-MeTMQ). Conjugated TMQ and conjugated MeTMQ with glucuronic acid were also found in the urine (8, 9).

It has been reported that 3-methoxyisoproterenol, a metabolite of isoproterenol (Iso), acts like an adrenergic β-receptor blocker. Thus it inhibits the positive chronotropic and vasodepressor responses to Iso in the dog and cat (10, 11). The antagonistic relationship between epinephrine or norepinephrine and the corresponding methoxymetabolites (metanephrine or normetanephrine) was also observed on the isolated guinea-pig tracheal muscle (12), on the isolated perfused rat heart (13), or on the non-pregnant uterus of the cat (14). On the other hand, the nictitating membrane of the cat, the seminal vesicle of the guinea-pig and the heart rate of the dog in situ were sensitized to epinephrine by metanephrine (14).

The present experiments were performed to investigate the possible adrenergic β-stimulating and β-blocking properties of the methoxymetabolites (6- and 7-MeTMQ) of TMQ, and the effects on the heart rate, blood pressure and histamine-induced bronchoconstriction were examined in the anesthetized cat. As to the conjugated metabolites with glucuronic acid, the experiments were not carried out in the present study, since their pharmacological activities were very weak, as examined on the isolated tracheal muscle of the guinea-pig, and also the acute toxicities of these metabolites were very low.

MATERIALS AND METHODS

1. Heart rate and blood pressure

Cats of both sexes weighing 2 to 3.5 kg were anesthetized with sodium pentobarbital (PB) (35 mg/kg) by intraperitoneal injection. Blood pressure was recorded from the femoral artery with pressure transducer. The heart rate was recorded by cardiotachography, triggered by the arterial pulse. The drug solution was injected into the cannulated femoral vein.
2. **Bronchoconstriction induced by histamine**

Cats anesthetized with PB (35 mg/kg, i.p.) were immobilized by intravenous injection of gallamine triethiodide (5 mg/kg) and maintained under artificial respiration. Ventilation was carried out with a constant volume respiratory pump through a tracheal cannula. Intratracheal pressure, the increase of which denotes the bronchoconstriction, was recorded by means of a pressure transducer connected to the side arm of the tracheal cannula. The bronchoconstriction was produced by the intravenous injection of histamine dihydrochloride (5 μg/kg). The drugs were injected into the femoral vein through the cannula.

![Chemical structures of TMQ, 6-MeTMQ and 7-MeTMQ.](Image)

**Fig. 1.** Chemical structures of TMQ, 6-MeTMQ and 7-MeTMQ.

3. **Drugs**

TMQ and its methoxymetabolites, 6- and 7-MeTMQ, were synthetized in our Organic Chemistry Research Laboratory. The chemical structures of these compounds are shown in Fig. 1. Although 6- and 7-methoxy compounds were derived from the racemate of TMQ, these derivatives were referred to as 6- and 7-MeTMQ in the present paper. Iso was supplied by Boehringer Sohn Co., Ltd. Propranolol (Pro) was the commercial product from the Imperial Chemical Industries Ltd.

**RESULTS**

1. **Cardiovascular actions**

1) **Effect on blood pressure and heart rate**

Intravenous injection of TMQ, in a dose of about 0.5 μg/kg, produced hypotensive and positive chronotropic effects in the anesthetized cat (6). On the other hand, 10 μg/kg of 6- and 7-MeTMQ exhibited little effects on the blood pressure and heart rate. When the doses were increased to 1 mg/kg, the blood pressure were decreased by 14±2.2% and 24±3.4%, while the heart rates were increased by 19±4.2% and 6±1.6% after the administration of 6- and 7-MeTMQ, respectively.

2) **Effect on positive chronotropic and hypotensive actions of Iso**

Tables 1 and 2 summarize the effects of 6-MeTMQ, 7-MeTMQ and Pro on the positive chronotropic and vasodepressor responses to Iso. Three min after pretreatment with the test compound, Iso was injected into the femoral vein of the cat. Like Pro, both 6-
and 7-MeTMQ antagonized to the effect of Iso. The results show that the methoxyme-
tabolites of TMQ act like an adrenergic β-receptor blocker. The blocking action of 6-
MeTMQ was about a tenth that of Pro, while 7-MeTMQ was less active than 6-MeTMQ.

3) Effect on positive chronotropic and hypotensive actions of TMQ

Pretreatment with 10 µg/kg of 6-MeTMQ produced about 50% reduction on both
the increase in heart rate and the decrease in blood pressure caused by 0.1 µg/kg of TMQ.
The same dose of 7-MeTMQ, however, did not show any effect on the actions of TMQ.

2. Histamine-induced bronchoconstriction

1) Effect on bronchoconstriction induced by histamine

The administration of TMQ by intravenous route strongly prevented the development
of bronchoconstriction induced by histamine. An example of the experiments is shown in Fig. 2. Histamine (5 μg/kg) was injected into the femoral vein before and after treatment with 0.1 μg/kg of TMQ.

Fig. 2 also illustrates the effects of 6- and 7-MeTMQ on histamine-induced bronchoconstriction. Three min after administration of the test compound (1 mg/kg), 5 μg/kg of histamine was injected at a given interval. As shown in the figure, both 6- and 7-MeTMQ reduced the bronchospasm induced by histamine, the effect of 7-MeTMQ being stronger than that of 6-MeTMQ. It was further observed in the figure that the intratracheal pressure without histamine was reduced by 6- and 7-MeTMQ.

Fig. 3 shows the dose-response relationships of the effects of the compounds on the histamine-induced bronchoconstriction. Ten μg/kg of 6-MeTMQ exerted a slight reduction on the constriction, whereas 7-MeTMQ produced hardly any effect on it. 7-MeTMQ in a high dose of 1 mg/kg, however, showed stronger bronchodilation than 6-MeTMQ of the same dose. Ten mg/kg of 6-MeTMQ also reduced the bronchoconstriction but its potency was lower than that of 1 mg/kg of 7-MeTMQ.

As shown in Fig. 4, the bronchodilator effect of 7-MeTMQ (1 mg/kg) was markedly

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**Fig. 2.** Effects of TMQ, 6-MeTMQ and 7-MeTMQ on the histamine-induced bronchoconstriction in the cat. H: histamine.
inhibited by pretreatment with Pro (1 mg/kg). This was also the case with TMQ or 6-MeTMQ. In addition, it is noticed from Fig. 4 that Pro strongly enhanced the histamine-induced bronchoconstriction, especially in its duration, whereas such a potentiation was not observed with either 6- or 7-MeTMQ (cf. Fig. 2).

2) Effect on bronchodilator action of Iso

Fig. 5A and B show the time courses of the effects of methoxymetabolites on the bronchodilation caused by Iso (0.1 μg/kg). The action of Iso on the histamine-induced bronchoconstriction was examined before and after treatment with the metabolite.

As shown in Fig. 5A and B, 10 μg/kg of 6- and 7-MeTMQ did not inhibit the bronchodilator action of Iso. In Fig. 5A, the action of Iso seems to be potentiated by pretreatment with 6-MeTMQ. This is ascribed to the weak but long-lasting bronchodilator effect of 6-MeTMQ. It was further observed that 1 mg/kg of 6-MeTMQ produced hardly any effect, but 10 mg/kg of the compound strongly depressed the bronchodilation caused by Iso. As already mentioned, 1 mg/kg of 7-MeTMQ itself produced a strong bronchodilator action. Therefore, the effect of 7-MeTMQ of a higher dose on the response to Iso was not examined.

Fig. 5C illustrates the effect of Pro on the bronchodilator action of Iso. The action of Iso was completely abolished by pretreatment with 10 μg/kg of Pro. The increase in intratracheal pressure after treatment with Pro was attributable to the intensifying action of Pro on the histamine-induced bronchoconstriction.

From these results, it is roughly estimated that the inhibitory action of 6-MeTMQ
on the response to Iso was less than one-hundredth that of Pro.

3) Effect on bronchodilator action of TMQ

The experiments were carried out to see whether or not the metabolite of TMQ inhibits the bronchodilator action of the parent compound. Ten μg/kg of 6- and 7-MeTMQ, which corresponds to 100 times of the effective dose of TMQ (0.1 μg/kg), was used. For reference, 0.1 μg/kg of TMQ strongly inhibited the histamine-induced bronchoconstriction. It produced approximately 70% reduction (cf. Fig. 2).

Fig. 6A and B show the time courses of the effects of 6- and 7-MeTMQ. These compounds did not inhibit the bronchodilator action of TMQ. Furthermore, it was found that even under the influence of a high dose of 6-MeTMQ (1 mg/kg), no remarkable effect was discernible.

On the contrary, 10 μg/kg of Pro produced a strong inhibitory effect on the action of TMQ (Fig. 6C).
DISCUSSION

The methoxymetabolites of TMQ, i.e., 6- and 7-MeTMQ, produced weak positive chronotropic and hypotensive actions as well as weak bronchodilator effect in the anesthetized cat. The bronchodilator effects of the metabolites were inhibited by pretreatment with adrenergic β-receptor blocker, Pro, suggesting that these compounds were acting as β-receptor stimulants. The bronchodilator action of 7-MeTMQ was stronger than that of 6-MeTMQ.

The cardiovascular and bronchodilator activities of 6- and 7-MeTMQ were considerably lower than those of their parent compound, TMQ. Their potencies were only about a ten-thousandth that of TMQ. Therefore, such a possibility should be excluded that TMQ may display its strong β-receptor stimulating action after being metabolized in the tissues.

It was observed that the bronchodilator actions of 6- and 7-MeTMQ did not diminish when reserpinized and adrenalectomized cats were used. This finding may indicate that these compounds would not exert their effects as catecholamine-releaser.

Besides having β-receptor stimulating qualities, the methoxymetabolites act like adrenergic β-receptor blocker. Thus the increase in heart rate and the decrease in blood pressure caused by Iso were inhibited by pretreatment with these compounds. The blocking action of 6-MeTMQ was about a tenth that of Pro, whereas 7-MeTMQ had a weaker inhibitory property than 6-MeTMQ. At a high dose (10 mg/kg), 6-MeTMQ also inhibited the bronchodilation induced by Iso. Its potency was, however, very low and found to be less than one hundredth that of Pro.

It is of interest to note that 6-MeTMQ (10 µg/kg) reduced the cardiovascular effect of Iso, whereas it exerted no inhibitory action on the bronchodilation caused by Iso. On the contrary, the same dose of Pro inhibited both the cardiovascular and bronchodilator actions of Iso. Thus it follows that 6-MeTMQ has a property of selective blockade of adrenergic β-receptor.

What is important to know is how the metabolite interacts with its parent compound. In the present study, it has been shown that 10 µg/kg of 6-MeTMQ, which corresponds to about several ten times of the effective dose of TMQ for β-receptor stimulation, exhibited no influence on the bronchodilator action of TMQ. On the other hand, the hypotensive and positive chronotropic actions of TMQ were diminished under the same conditions as above. Ten µg/kg of 7-MeTMQ inhibited neither cardiovascular nor bronchodilator action of TMQ. In addition, it was found that 6- and 7-MeTMQ did not intensify the histamine-induced bronchoconstriction but prevent it. Therefore, it can be said that the protective action of TMQ on the experimental asthma is not inhibited by its methoxy-metabolites, and that the metabolites did not produce increasing airway obstruction.

SUMMARY

The effects of methoxymetabolites (6- and 7-MeTMQ) of trimetoquinol (TMQ) on the heart rate, blood pressure and histamine-induced bronchoconstriction were investi-
gated in the anesthetized cat. The positive chronotropic, hypotensive and bronchodilator activities of metabolites were considerably lower than that of their parent compound, TMQ. The blocking action of 6-MeTMQ on the cardiovascular effect of isoproterenol (Iso) was about a tenth that of propranolol, whereas 7-MeTMQ had a weaker inhibitory property than 6-TMQ. At a dose of 10 μg/kg, 6-MeTMQ inhibited the cardiovascular but not the bronchodilator responses to TMQ and Iso. Ten μg/kg of 7-MeTMQ inhibited neither cardiovascular nor bronchodilator actions of TMQ and Iso.

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