Short communications

The muscle relaxant activity of methaqualone and its methyl congener

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Studies with methaqualone and dimethylquinazolone showed them to possess both central and peripheral muscle relaxant activity, the latter only at high dose levels. They selectively inhibited polysynaptic reflexes and were more potent than mephenesin.

Introduction.—The hypnotic activity of methaqualone, 2-methyl-3- (2-methylphenyl)-4-quinazolone was first reported in 1955 (Gujral & Kohli) and the compound is now extensively used clinically as a non-barbiturate hypnotic. Methaqualone (MQ) also depresses polysynaptic spinal reflexes (Swift, Dickens & Becker, 1960) and the present report deals with its muscle relaxant activity compared with dimethylquinazolone (DMQ).

Methods.—Behavioural effects of intravenous doses of MQ and DMQ were studied in rabbits. The Straub's tail response induced by subcutaneous injection of dihydroxycodeinone pectinate (Proladone, Crooks, 10 mg/kg) was employed as a test to distinguish between centrally and peripherally acting muscle relaxants (Srimal, Jaitly & Bhargava, 1965).

Somatic reflex studies were performed on cats of either sex weighing 2·5–4·0 kg anaesthetized with chloralose (80 mg/kg i.v.), routinely vagotomized and maintained on positive pressure artificial respiration. In some of the cats, spinal transection was done under ether anaesthesia. These procedures have been described in earlier communications from this laboratory (Bhargava & Srivastava, 1965; Bhargava, Sinha & Tangri, 1966).

For the intracerebroventricular injection of drugs, a stainless steel cannula was implanted into a lateral cerebral ventricle according to the method of Feldberg & Sherwood (1954).

The solutions of MQ and DMQ were made in propylene glycol. Control effects of the vehicle were obtained in all experiments. Mephenesin (Myanesin, B.D.H.) was employed as a standard drug.

Results—*Behavioural studies.* Both MQ (6·0 mg/kg) and DMQ (1·0 mg/kg) retarded locomotor activity and induced hind limb weakness and ataxia in rabbits whilst slightly higher doses (MQ, 10·0 mg/kg and DMQ, 3·0 mg/kg) induced flaccid paralysis, relaxation of abdominal muscles, loss of righting reflex and pinneal reflex.

The approximate LD50 of MQ and DMQ in mice were found to be 180 mg/kg i.p. and 85 mg/kg i.p. respectively.

The Straub's tail response was not affected by MQ (10–15 mg/kg) and DMQ (5–10 mg/kg) which induced ataxia and hind limb weakness but higher doses (MQ=30–60 mg/kg and DMQ=20–25 mg/kg) which also produced loss of righting reflex and head drop, abolished it.

Somatic reflex studies

Intact cats.—Intravenous injections of both MQ (0·5–10·0 mg/kg) and DMQ (0·5–5·0 mg/kg) selectively inhibited the linguomandibular polysynaptic reflex (LMR) without affecting the patellar monosynaptic reflex (see Table 1). Similar results were observed on intraventricular administration as well. The ED50 (mg/kg) by the intracerebroventricular route of MQ and DMQ for inhibiting the LMR were 1·66 and 0·57 respectively, compared with 5·25 and 2·04 intravenously. Both polysynaptic facilitation and inhibition of the patellar reflex, elicited by electrical stimulation of dorsolateral facilitatory and ventromedial inhibitory areas of reticular formation were inhibited by MQ (10 mg/kg i.v.) and DMQ (5 mg/kg i.v.).

In spinal cats MQ (10 mg/kg i.v.) and DMQ (5 mg/kg i.v.) inhibited both polysynaptic facilitation and inhibition without affecting the amplitude of the patellar reflex.

In another series of experiments the effect of MQ, DMQ and mephenesin was studied on gastrocnemius responses induced by sciatic nerve stimulation. All the three compounds in higher doses were found to inhibit the response of the muscle. The ED50 (mg/kg) to produce

TABLE 1. *Comparative* ED50's *of mephenesin, methaqualone and dimethylquinazolone to inhibit the linguomandibular reflex and sciatic gastrocnemius response*

Compounds	Central muscle relaxant activity		Peripheral muscle relaxant activity		Relative muscle relaxant activity peripheral/central
	Linguomandibular reflex		Sciatic gastrocnemius response		
	ED50 (mg/kg) ±S.E.	Activity ratio	ED50 (mg/kg) ±S.E.	Activity ratio	
Mephenesin	17·38±0·045	1	87·10±0·130	1	5
Methaqualone	5·25±0·085	3·31	36·31±0·085	2·04	7
Dimethylquinazolone	2·04±0·032	8·51	5·67±0·142	15·36	3

this effect was found to be: MQ 36·31, DMQ 5·67 and mephenesin 87·10 (Table 1).

Discussion.—It can be seen from the results on gross behaviour that low doses of MQ and DMQ induce ataxia, and hind limb weakness. These doses neither produce head drop nor abolish the Straub's tail response. These findings are suggestive of a muscle relaxant component of central origin in these compounds. High doses of these agents in addition caused loss of righting reflex, head drop and antagonized Straub's tail response thereby suggesting a pheripheral muscle relaxant component as well. Thus it may be inferred that these compounds possess central muscle relaxant activity but at higher doses a peripheral neuromuscular action comes into play.

The results of the study with somatic reflexes demonstrate an inhibitory action of DMQ and MQ on polysynaptic pathways. Moreover, the agents had greater affinity for polysynaptic pathways of the brain stem than the spinal cord. The linguomandibular reflex, a polysynaptic reflex mediated at the brain stem level was selectively inhibited by these compounds (administered intravenously or intracerebroventricularly) without affecting spinal monosynaptic patellar reflex. It may be concluded that the effects of MQ and DMQ qualitatively resemble those of mephenesin on the somatic reflexes.

Quantitative comparison of the central muscle relaxant activity on the basis of the inhibition of the linguomandibular reflex shows that on intravenous administration both MQ and DMQ were 3·31 and 8·51 times more active than mephenesin (Table 1). By the intraventricular route, as well, DMQ was more potent than MQ in inhibiting this reflex. However both these compounds had a higher peripheral/central muscle relaxant activity ratio than mephenesin (Table 1).

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REFERENCES

BHARGAVA, K. P. & SRIVASTAVA, R. K. (1965). Anti-tetanus activity of central muscle relaxants. *Br. J. Pharmac. Chemother.*, **25**, 74–80.

BHARGAVA, K. P., SINHA, J. N. & TANGRI, K. K. (1966). A neuropharmacological study of the antidepressant action of imipramine. *Br. J. Pharmac. Chemother.*, **27**, 468–478.

FELDBERG, W. & SHERWOOD, S. L. (1954). Injections of drugs into the lateral ventricle of the cat. *J. Physiol., Lond.*, **123**, 148–167.

GUJRAL, M. L. & KOHLI, R. P. (1955). A preliminary report on some new synthetic narcotics. *J. Ass. Physns India*, **2**, 29–35.

SRIMAL, R. C., JAITLY, K. D. & BHARGAVA, K. P. (1965). Effect of muscle relaxants on the Straub tail phenomenon. *Jap. J. Pharmac.*, **15**, 332–334.

SWIFT, J. G., DICKENS, E. A. & BECKER, B. A. (1960). Anticonvulsant and other pharmacological activities of tuazolone. *Archs int. Pharmacodyn. Thér.*, **128**, 112–125.

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