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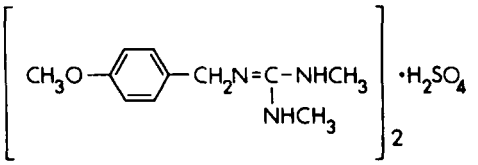
# COMMUNICATIONS

## Meobentine sulphate (bis[*N*-4-methoxybenzyl-*N'N''*-dimethylguanidine]sulphate): a new antidysrhythmic agent

W. B. WASTILA*, F. C. COPP, E. WALTON, C. H. ELLIS, R. A. MAXWELL, *Wellcome Research Laboratories, Department of Pharmacology, Research Triangle Park, NC 27709, U.S.A. and Chemical Research Laboratory, Beckenham, Kent, BR3 3BS, U.K.*

Bretylium has several drawbacks as an antidysrhythmic agent (see Bigger & Hoffman 1980). It is a potent adrenergic neuron blocking agent (Boura & Green 1959; Smirk & Hodge 1959; Dollery et al 1960). As a result it produces severe orthostatic hypotension. It also may cause sympathomimesis by the release of noradrenaline from nerve endings (Gilmore & Siegel 1962). Furthermore, since it is a quaternary ammonium salt, it is poorly and erratically absorbed from the gastrointestinal tract.

As a result of these shortcomings, a search was instituted to find a compound which retained the antidysrhythmic properties of bretylium and which like bretylium (Namm et al 1975) accumulated in the myocardium but which did not produce sympathomimesis or adrenergic neuron blockade. Additionally, we sought a compound with a structure which would allow for the possibility of better and more predictable absorption from the gastrointestinal tract than is achieved with bretylium, and for the absence of c.n.s. effects. Meobentine sulphate (Rythmatine) which was synthetized by one of the authors (E.W.) meets these criteria and has the following structure:



The pharmacological properties of meobentine to date have been reported only in abstract form by Touw et al (1977) and Wang et al (1977). A description of the pharmacology of the drug follows. The doses are expressed as those of the salt.

*Antidysrhythmic effects*

*Fibrillation after coronary occlusion and release in vivo.* Nine of 17 0·9% NaCl(saline)-treated dogs fibrillated during the 20 min occlusion period while the remaining eight dogs fibrillated immediately upon release of the occlusion. Intravenous meobentine, at 5–20 mg $kg^{-1}$ to 18 dogs and oral meobentine, at 70 mg $kg^{-1}$ for 3–5 days to 6 dogs, significantly protected against ventricular fibrillation (Table 1.)

*Fibrillation after coronary occlusion and reperfusion in vitro.* In the Langendorff rat heart preparation meobentine at $3 \times 10^{-7}$ to $1 \times 10^{-5}$ M produced a concentration-dependent decrease in the incidence of ventricular fibrillation (Table 2) observed after 15 min occlusion and reperfusion of the left coronary artery.

A significant dose-dependent decrease in ventricular fibrillation was also observed in hearts removed from rats given meobentine 12·5 to 100 mg $kg^{-1}$ i.p. (Table 2).

*Electrically-induced fibrillation.* Meobentine (10–40 mg $kg^{-1}$ i.v.) increased the ventricular fibrillation threshold in dogs anaesthetized with Dial-urethane (Table 3). The onset of activity occurred within 1 h and lasted an average of 3 h. As with bretylium (Bacaner et al 1969), the effects on fibrillation threshold were variable at all dose levels. Significant increases in threshold were observed at the 20 and 40 mg $kg^{-1}$ doses (Table 3). Meobentine appeared to

Table 1. Antifibrillatory effect of meobentine after a 20-minute occlusion of the left anterior descending coronary artery in anaesthetized dogs. Method: dogs were anaesthetized with pentobarbitone sodium, 30 mg $kg^{-1}$ i.v. The heart was exposed by a thoracotomy and suspended in a pericardial cradle. The left anterior descending coronary artery was dissected free as close to its origin as possible. A snare-ligature was placed around the coronary artery to allow acute total occlusion of the left anterior descending coronary and the first septal branch. In these experiments the vessel was occluded for 20 min and then released. Meobentine was administered intravenously 1 h before coronary artery occlusion. The last dose of orally administered meobentine was given 1·5 h before coronary artery occlusion.

| | | No. fibrillating during occlusion | No. fibrillating on release of occlusion | No. surviving |
|---|---|---|---|---|
| Control Meobentine | n = 17 | 9 | 8 | 0 |
| 5 mg $kg^{-1}$ i.v. | n = 6 | 0 | 5 | 1* |
| 10 mg $kg^{-1}$ i.v. | n = 6 | 1 | 3 | 2* |
| 20 mg $kg^{-1}$ i.v. | n = 6 | 0 | 4 | 2* |
| 70 mg $kg^{-1}$ p.o. × 3–5 days | n = 6 | 1 | 3 | 2* |

* Chi square analysis with Yates' correction, $P < 0.05$.

* Correspondence.

Table 2. Effect of meobentine on ventricular fibrillation after coronary artery occlusion and reperfusion in rat isolated hearts according to Lubbe et al (1978).

| | | No. fibrillating after release | No. not fibrillating after release |
|---|---|---|---|
| (a) 1st Experiment | | | |
| Control Meobentine | (n = 11) | 9 | 2 |
| $3 \times 10^{-7}$ M | (n = 10) | 8 | 2 |
| $1 \times 10^{-6}$ M | (n = 10) | 6 | 4* |
| $3 \times 10^{-6}$ M | (n = 11) | 0 | 11* |
| $1 \times 10^{-5}$ M | (n = 10) | 1 | 9* |
| (b) 2nd Experiment | | | |
| Control Meobentine | (n = 11) | 10 | 1 |
| 12·5 mg kg$^{-1}$ i.p. | (n = 6) | 5 | 1 |
| 25 mg kg$^{-1}$ i.p. | (n = 6) | 4 | 2 |
| 50 mg kg$^{-1}$ i.p. | (n = 6) | 2 | 4* |
| 100 mg kg$^{-1}$ i.p. | (n = 6) | 0 | 6* |

(a) Meobentine added to Krebs-Henseleit solution and perfused for 45 min before coronary artery reperfusion after a 15 min occlusion.
(b) Isolated hearts from rats pretreated (30 min) with meobentine.
* Chi square analysis with Yates' correction, $P < 0.05$.

be more effective by the intramuscular than by the intravenous route (Table 3).

Spontaneous recovery of the dog ventricle from electrically-induced fibrillation is rare. Table 4 shows that after meobentine (20–40 mg kg$^{-1}$), and also bretylium (as reported by Bacaner et al 1969), an incidence of reversion of ventricular fibrillation to normal sinus rhythm occurred without the use of direct current countershock.

*Chloroform-induced fibrillation.* Four inhibitors of the sympathetic nervous system (guanethidine, propranolol, hexamethonium and bretylium) were effective and potent (ED50s: 0·6, 3·4, 8 and 7 mg kg$^{-1}$, respectively) in protecting mice against chloroform-induced fibrillation (method of Lawson 1968). Relative to these agents, meobentine (ED50 = 56 mg kg$^{-1}$ i.p.) was weakly active as were three known antiarrhythmic agents (quinidine, 75 mg kg$^{-1}$; lidocaine, > 45 mg kg$^{-1}$ and procainamide 150 mg kg$^{-1}$).

*Ouabain-induced dysrhythmias.* Intravenous infusion of ouabain (method of Kato et al 1974) to 7 control dogs at 2·5 μg kg$^{-1}$ min$^{-1}$ produced the first detectable ventricular arrhythmias at 75·9 ± 2·4 μg kg$^{-1}$ (mean ± s.e.) and ventricular fibrillation at 129·2 ± 8·2 μg kg$^{-1}$. After 15 mg kg$^{-1}$ i.v. meobentine 30 min before ouabain infusion, the first arrhythmias required 97·3 ± 6·0 μg kg$^{-1}$ and fibrillation 152·5 ± 4·0 μg kg$^{-1}$ ouabain. Both changes were significant ($P < 0.05$).

In another experiment 5 saline-treated dogs fibrillated after a cumulative dose of 112·5 ± 4·5 μg kg$^{-1}$, whereas, the meobentine, 15 mg kg$^{-1}$ i.v. given immediately after the onset of the first arrhythmias, increased the dose of ouabain needed to produce ventricular fibrillation to 139·6 ± 7·1 μg kg$^{-1}$. The difference was significant ($P < 0.05$).

*Dysrhythmias due to coronary artery ligation.* Meobentine given to conscious dogs 24 h after coronary artery ligation (method of Harris, 1950) at 30 mg kg$^{-1}$ i.v., infused at 2·5 mg kg$^{-1}$ min$^{-1}$, also produced a prompt antidysrhythmic effect lasting for > 60 min. Touw et al (1977) also reported meobentine to have a prolonged, dose-dependent, antidysrhythmic activity in anaesthetized dogs at 24 h.

*Cardiovascular effects*

Meobentine given as i.v. boluses in 5 closed-chested dogs under Dial-urethane had minimal effects on arterial pressure and heart rate except for a 20–25% increase in heart rate after 5 and 10 mg kg$^{-1}$ and a transient 10·15% decrease after 20 mg kg$^{-1}$ (cumulative dose = 35 mg kg$^{-1}$).

Repeated 10 mg kg$^{-1}$ i.v. bolus of meobentine (cumulative dose = 60 mg kg$^{-1}$) produced variable transient changes in mean arterial pressure, heart rate, stroke volume and total peripheral resistance. Over the full course of the experiment (240 min) the cumulative, intravenous dose of 60 mg kg$^{-1}$ was without serious, sustained deleterious effect on the circulation.

Cardiovascular changes peaked by the end of a 10 min i.v. infusion of 10 mg kg$^{-1}$ meobentine in 5 open-chested dogs under morphine-chloralose. Mean arterial pressure and cardiac output increased less than 5% while heart rate transiently increased 45% in these high vagotonic dogs and total peripheral resistance did not change. All values rapidly returned to control.

*Autonomic effects*

Serial administration of 5, 10 and 20 mg kg$^{-1}$ i.v. meobentine had negligible effect on the responses of the

Table 3. Peak effect of increasing doses of meobentine and bretylium on the threshold for electrically-induced fibrillation of the dog ventricle by the method of Bacaner et al (1969).

| Compound | Dose mg kg$^{-1}$ | Animals | Pre-drug threshold ± s.e. mamp | Post-drug threshold ± s.e. mamp | % Change | $P$ |
|---|---|---|---|---|---|---|
| Meobentine (intravenous) | 0 | 10 | 32 ± 3 | 35 ± 3 | 9 | >0·5 |
| | 5 | 4 | 32 ± 5 | 43 ± 5 | 31 | 0·15 |
| | 10 | 5 | 34 ± 2 | 44 ± 7 | 29 | 0·2 |
| | 20 | 5 | 32 ± 4 | 52 ± 4 | 63 | <0·01 |
| | 40 | 5 | 36 ± 7 | 62 ± 2 | 72 | 0·01 |
| Bretylium (intravenous) | 10 | 5 | 42 ± 6 | 32 ± 4 | −24 | 0·17 |
| | 20 | 11 | 47 ± 3 | 68 ± 5 | 45 | 0·01 |
| Meobentine (intramuscular) | 0 | 10 | 32 ± 3 | 35 ± 8 | 9 | >0·5 |
| | 5 | 3 | 37 ± 3 | 47 ± 3 | 27 | 0·07 |
| | 10 | 3 | 20 ± 0 | 47 ± 3 | 135 | <0·01 |
| | 20 | 1 | 40 | 70 | 75 | — |
| | 40 | 1 | 30 | 80 | 165 | — |

nictitating membrane to stimulation of the postganglionic cervical sympathetic trunk in cats (n = 4) anaesthetized with pentobarbitone. In only three of 10 cats anaesthetized with chloralose was the pressor response to carotid occlusion partially blocked by a cumulative meobentine dose of 35 mg $kg^{-1}$. The fall in the arterial blood pressure in response to head-up vertical tilt was not affected by a cumulative dose of 35 mg $kg^{-1}$ meobentine. Meobentine, $10^{-3}$ M, depressed the muscle but did not block the response to nerve stimulation of the isolated adrenergic nerve-intestinal smooth muscle preparation of Finkleman (1930). Meobentine had no effect on the noradrenaline content of rat heart 8 and 24 h after i.p. doses of 12·3 and 18·7 mg $kg^{-1}$. Furthermore, bradycardia produced by peripheral vagal nerve stimulation was not affected by 5–20 mg $kg^{-1}$ i.v. meobentine in 4 cats anaesthetized with pentobarbitone.

Table 4. Effect of meobentine and bretylium on the incidence of spontaneous defibrillation in the dog by the method of Bacaner et al (1969).

| Dose mg $kg^{-1}$ | Meobentine No. reverting / No. treated | Meobentine % reverting | Bretylium No. reverting / No. treated | Bretylium % reversion |
|---|---|---|---|---|
| 0* | 0/18 | 0 | 0/28 | 0 |
| 5 | 0/3 | 0 | 0/2 | 0 |
| 10 | 0/5 | 0 | 0/4 | 0 |
| 20 | 2/5 | 40 | 2/18 | 11 |
| 40 | 3/5 | 60 | 1/4 | 25 |

* The control figures represent the aggregate of the pre-drug control measurement of all the animals used at the several doses listed.

Meobentine was without direct activity in guinea-pig ileum and rabbit atria and aortic strips at $10^{-7}$ and $10^{-4}$ M. It had little or no effect at $10^{-7}$ to $10^{-4}$ M on concentration-response curves of (1) isoprenaline in rabbit atria, (2) noradrenaline in rabbit aorta, (3) acetylcholine and histamine in guinea-pig ileum, the guinea-pig method of Bülbring & Wajda (1945) indicated that meobentine was approximately four times less potent as lidocaine as a local anaesthetic but had a much longer duration of action. Wang et al (1977) reported that meobentine, at $1 \times 10^{-5}$ M and higher, had a local anaesthetic-like activity on isolated atrial and ventricular muscles of rat and canine Purkinje fibres.

*Myocardial levels of meobentine.* In the rat isolated heart, (method of Lubbe et al 1978) the infusion of [$^{14}$C]meobentine at $1 \times 10^{-6}$ and $1 \times 10^{-5}$ M resulted in meobentine levels of $2{\cdot}4 \times 10^{-5}$ and $2{\cdot}2 \times 10^{-4}$ M (calculated as mol $kg^{-1}$ of myocardium) respectively. As noted in Table 2a, ventricular fibrillation was reduced 40 and 90%, respectively, as a result of infusion of $1 \times 10^{-6}$ and $1 \times 10^{-5}$ M meobentine. The > 20-fold myocardial accumulation of meobentine over perfusate concentration agrees well with our earlier report (Touw et al 1977) of the in vivo mycocardium:plasma ratios obtained in dogs, namely $8{\cdot}7 \times 10^{-5}$:$4{\cdot}7 \times 10^{-6}$ M after 5 mg $kg^{-1}$ i.v.

Levels of meobentine in isolated perfused rat hearts 30 min after pretreatment with [$^{14}$C]meobentine at 12·5 and 50 mg $kg^{-1}$ i.p. were $3{\cdot}2 \times 10^{-5}$ and $1{\cdot}8 \times 10^{-4}$ M, respectively. At these doses the incidence of ventricular fibrillation was reduced by 17 and 67%, respectively (Table 2b). The meobentine concentrations in myocardium during antidysrhythmic activity in these experiments, and in coronary artery ligated dogs (Touw et al 1977) were approximately the same as the perfusate concentration producing electrophysiological effect in isolated cardiac tissue, i.e. > $10^{-5}$ M (Wang et al 1977; Touw et al 1977).

Thus, meobentine, a compound chemically dissimilar from other antiarrhythmic agents, has antidysrhythmic and antifibrillatory activity in several diverse models. It is not an inhibitor of the sympathetic nervous system. It is not cholinolytic nor sympathomimetic and does not deplete noradrenaline stores. The cardiovascular effects observed after intravenous administration of effective antidysrhythmic doses are minimal and of short duration compared with the duration of its antidysrhythmic activity. The data suggest that the antidysrhythmic action is due to the accumulation and retention of meobentine in the myocardium.

Meobentine which is '*p*-methoxy-bethanidine' is structurally very similar to the guanidine neuron blocking agent, benthanidine. Guanidine blocking agents are better and more reliably absorbed than quaternary ammonium blocking agents in man (Maxwell & Wastila 1977). Therefore, meobentine is expected to have reasonable absorption in man following oral administration and, like bretylium, because it is a highly charged molecule which penetrates the brain poorly, will have little c.n.s. side effect. Meobentine is currently undergoing clinical evaluation in man.

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