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Muscle Relaxant Activity of Methocarbamol Enantiomers in Mice*

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Abstract

Documented studies support the emerging idea that drug enantiomers could have different pharmacological activity. Our bibliographical data have shown that so far no report has been published on the pharmacological activity of individual enantiomers of methocarbamol.

This study was conducted to characterize the muscle relaxant activity of methocarbamol enantiomers. The rotarod test was used to compare the muscle relaxant activity of racemic methocarbamol and pure enantiomers after intraperitoneal administration of the enantiomers to mice.

The results show that (+)- *R*-methocarbamol has higher muscle relaxant activity compared with racemic methocarbamol or (−)- *S*-methocarbamol.

Many drugs act on the central nervous system to produce skeletal muscle relaxation as a primary or secondary pharmacological effect. Methocarbamol is a well known centrally active skeletal muscle relaxant which has been commercially available for over three decades (White 1995). It is formulated as a single entity or in combination with other analgesics such as acetylsalicylic acid (aspirin), acetaminophen (paracetamol) and codeine. Methocarbamol is a chiral drug which is clinically used as a racemic mixture of 50% (+)- *R*- and 50% (−)- *S*-enantiomer. In the past 20 years studies have shown that drug enantiomers may possess different pharmacodynamic characteristics; frequently only one possesses the desired therapeutic activity, while the other may be inactive or even harmful (Drayer 1986). Drug enantiomers can also have different pharmacokinetic properties (Drayer 1986; Jamali et al 1989; Tucker & Lennard 1990). Therefore, the pharmacologic activity of the individual enantiomers should be characterized for the principle and other important pharmacologic effects (Heydorn 1995).

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Based on our bibliographic knowledge, so far no report has been published on the different pharmacodynamic properties of the methocarbamol enantiomers. This study was conducted to characterize the muscle relaxant activity of the methocarbamol enantiomers.

Materials and Methods

Animals

Male albino mice (22–27 g) were trained to remain on a rotarod for 120 s twice daily. Those animals able to remain on the rotarod for this time were selected for the experiments.

Apparatus

The rotarod apparatus (Model 7650, UGO Basile, 21025 Comerio-Varese, Italy) consisted of a plastic drum (3 cm diam., 30 cm long) with a non-slippery surface. The drum was divided into five equal sections by four discs, enabling five mice to walk on the drum at the same time. The rotarod test was performed as indicated by Dunham & Miya (1957) and the rotarod speed was 10 rev min^{-1}.

Drugs

Racemic methocarbamol (Whitehall-Robins, Mississauga, Canada), (+)- *R*-methocarbamol and (−)- *S*-methocarbamol (Lee Labs, Petersburg, VA,) were kindly donated by Dr F. Jamali (University of Alberta, Edmonton, Alberta, Canada).

Test solutions were prepared in a 25% solution of polyethylene glycol 300 (Aldrich, Milwaukee, WI) in distilled water.

Procedure

The mice were divided into groups of seven and were dosed with either racemic methocarbamol (25, 50, 100, 150 or 200 mg kg^{-1}), (+)- *R*-methocarbamol (12·5, 25, 50 or 100 mg kg^{-1}), (−)- *S*-methocarbamol (25 mg kg^{-1}), or vehicle (polyethylene glycol in water) intraperitoneally, with a maximum injection volume of 5 mL kg^{-1}. The mice were placed on the roller at 0, 15, 30, 45 and 60 min after injection. The time taken for each mouse to fall off the rotarod was recorded as the endurance time. Total endurance time was calculated during 60 min after drug administration. All tests were conducted between 0830 and 1130 h. Changes of endurance times among different groups were noted.

Data analysis

The mean ± s.e.m. of the endurance time and total endurance time were calculated for each group of mice. Analysis of variance followed by Newman-Keuls test was performed.

Results and Discussion

Comparing the endurance time of racemic methocarbamol-treated mice (25, 50, 100, 150 and 200 mg kg^{-1}) with the vehicle-treated group, showed a significant difference ($P < 0{\cdot}01$) in the muscle relaxant activity. The maximum response was achieved at 75 min with 200 mg kg^{-1} racemic methocarbamol (Figure 1A). The mean ± s.e.m. of total endurance time of each dose of racemic methocarbamol was significantly ($P < 0{\cdot}01$) lower than the control group.

Similar results were observed using (+)- *R*-methocarbamol (12·5, 25, 50 and 100 mg kg^{-1}), with a maximum response at 100 mg kg^{-1} (Figure 1B). The mean ± s.e.m. of total endurance time of each dose of the (+)- *R*-enantiomer was significantly ($P < 0{\cdot}01$) lower than the vehicle-treated group. As seen in Figure 1B, the muscle relaxant activity of 50 mg kg^{-1} of the (+)- *R*-enantiomer

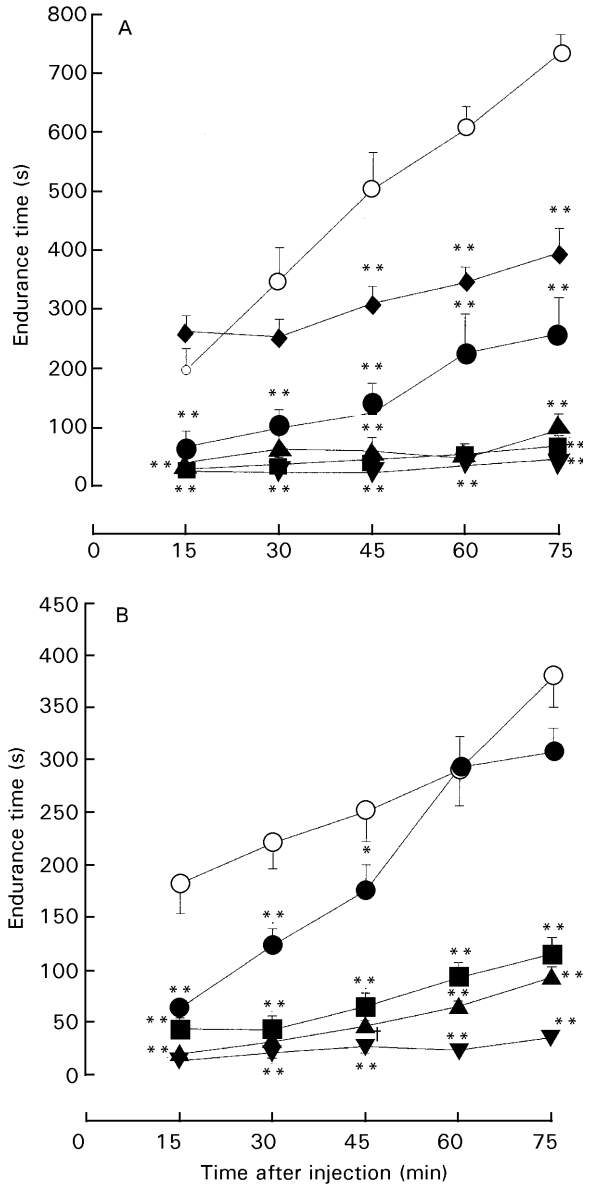

Figure 1. Time-course effects of racemic methocarbamol (A) and (+)- *R*-methocarbamol (B) induced muscle relaxation in mice. Animals were injected intraperitoneally with vehicle (○) or racemic methocarbamol (◆25, ●50, ▲100, ■150 or ▼200 mg kg^{-1}), or (+)- *R*-methocarbamol (●12·5, ■25, ▲50 or ▼200 mg kg^{-1}). Muscle relaxation was recorded at 15-min intervals. Each point is the mean ± s.e.m. of seven animals during 15 min. *$P < 0{\cdot}05$ and **$P < 0{\cdot}01$ were considered significant.

was lower than the 25 mg kg^{-1} dose. This variation may be due to the saturation of the receptors or possible involvement of other non-specific mechanisms. Comparing the data obtained for racemic methocarbamol with (+)- *R*-methocarbamol showed that the (+)- *R*-enantiomer had the greater activity.

Results achieved for racemic methocarbamol, (+)- *R*-methocarbamol and (−)- *S*-methocarbamol at 25 mg kg^{-1}, showed minimum and maximum

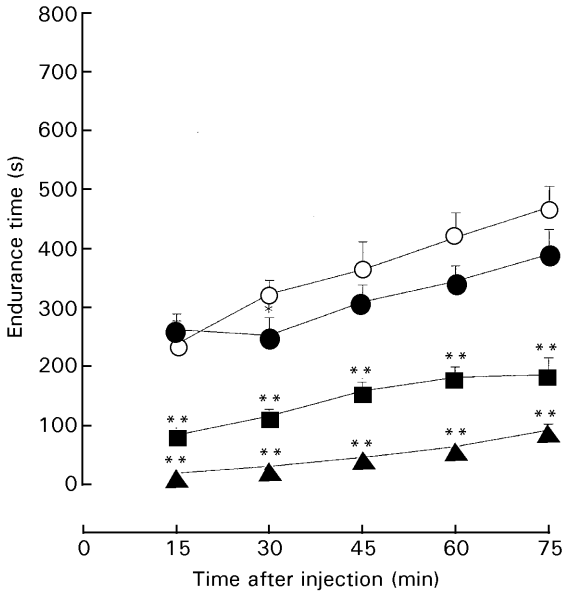

Figure 2. Muscle relaxation activity induced by 25 mg kg^{-1} racemic methocarbamol (●), (−)- *S*-methocarbamol (■), (+)- *R*-methocarbamol (▲) and vehicle (○). Endurance time was recorded at 15-min intervals. Each point is the mean ± s.e.m. of seven animals during 15 min. *$P < 0.05$, **$P < 0.01$ was considered significant.

responses of racemic and (+)- *R*-methocarbamol, respectively (Figure 2). The mean ± s.e.m. of total endurance time for the (+)- *R*-enantiomer was significantly ($P < 0.01$) lower than for racemic or (−)- *S*-methocarbamol.

Compared with the (−)- *S*-enantiomer, the (+)- *R*-enantiomer has greater muscle relaxant activity. This may be due to the different distribution, metabolism or receptor binding of the enantiomers, and remains to be studied.

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