Title: THIOPENTAL ANTAGONIZES MORPHINE-MIDAZOLAM HYPNOTIC SYNERGISM

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Introduction. The degree of synergism regarding the hypnotic effect with a morphine-midazolam-thiopental combination is less than that with a morphine-midazolam combination.[1] The difference between outcomes for the triple and binary anesthetic combinations suggests that thiopental competes with midazolam and/or morphine for a mechanism providing morphine-midazolam synergistic interaction regarding hypnotic effect. The aim of the present study was to confirm that thiopental antagonizes morphine-midazolam hypnotic synergism and to find out whether thiopental competes with morphine or midazolam for the mechanism providing this synergism.

Methods. Experiments were performed on male Sprague-Dawley rats weighing 225-275 g. Loss of the righting reflex was used as an index of the hypnotic action. In one series of experiments, the effects of morphine (0.6 $mg \cdot kg^{-1}$, 1/50 of ED_{50} for loss of the righting reflex) or morphine (0.6 $mg \cdot kg^{-1}$)-thiopental (0.1 $mg \cdot kg^{-1}$) combination on the midazolam dose-response curve for loss of the righting reflex were studied. In another series, the effects of midazolam (0.2 $mg \cdot kg^{-1}$, 1/50 of ED_{50} for loss of the righting reflex) or midazolam (0.2 $mg \cdot kg^{-1}$)-thiopental (0.1 $mg \cdot kg^{-1}$) combination on the midazolam dose-response curve for loss of the righting reflex were investigated. In each series, three dose-response curves (three groups of experiments) were determined: without interacting drugs, with interacting drug, and with two interacting drugs including thiopental (Tables 1 and 2). The experiments were carried out in a clear chamber where oxygen was delivered. Each animal was given only one predetermined dose of a drug or drug combination. The drugs were injected into the saphenous vein over 60 seconds. Total injected volume did not exceed 0.8 ml. When used in combination, drugs were injected so that synchronization of the peak effects would occur. Twenty animals were used to determine the dose-response curve for a drug or drug combination in each group of experiments with doses equally spread to give a range of doses that block the righting reflex in none or all of the animals in a subgroup. Dose-response curves and ED_{50} values were determined with the use of probit analysis.[2]

Results. Morphine (0.6 $mg \cdot kg^{-1}$) reduced the midazolam ED_{50} value for loss of the righting reflex from 11.2 $mg \cdot kg^{-1}$ to 1.6 $mg \cdot kg^{-1}$ ($p<0.0001$). The shift in the midazolam ED_{50} value was markedly reduced (from 1.6 $mg \cdot kg^{-1}$ to 6.3 $mg \cdot kg^{-1}$, $p<0.005$) by thiopental, 0.1 mg·kg-1 (Table 1). Midazolam (0.2 $mg \cdot kg^{-1}$) reduced the morphine ED_{50} value for loss of the righting reflex from 34.5 $mg \cdot kg^{-1}$ to 6.8 $mg \cdot kg^{-1}$ ($p<0.0001$). The addition of thiopental (0.1 $mg \cdot kg^{-1}$) to midazolam did not change the shift in the morphine ED_{50} value (Table 2).

Conclusion. Thiopental reduces morphine-midazolam hypnotic synergism by competing with morphine for a mechanism responsible for the morphine-midazolam interaction.

Table 1. Effect of morphine and morphine-thiopental combination on the hypnotic action of midazolam

Group	Interacting drug ($mg \cdot kg^{-1}$)	Midazolam ED_{50} in $mg \cdot kg^{-1}$ (95% conf.limits)	Potency ratio
A	None	11.2 (5.9, 27.6)	1
B	Morphine (0.6)	1.6 (0.1, 3.8)[a]	7.0
C	Morphine (0.6) and Thiop.(0.1)	6.3 (4.2, 52.5)[b]	1.8

a = diff. from A at $p<0.0001$, b = diff. from B at $p<0.005$

Table 2. Effect of midazolam and midazolam-thiopental combination on the hypnotic action of morphine

Group	Interacting drug ($mg \cdot kg^{-1}$)	Morphine ED_{50} in $mg \cdot kg^{-1}$ (95% conf.limits)	Potency ratio
A	None	34.5 (20.8, 132.1)	1
B	Midazolam (0.2)	6.8 (4.2, 9.8)[a]	5.1
C	Midazolam (0.2) and Thiop.(0.1)	6.2 (3.6, 8.9)[a]	5.5

a = diff. from A at $p<0.0001$

References.

1. Kissin I, Brown PT, Bradley EL Jr, Salazar CH. Morphine-midazolam-thiopental hypnotic interaction in rats. Fed Proc 47:1200, 1988.

2. Finney DJ. Probit Analysis. London, Cambridge, University Press, 1952.

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