COMPARISON OF SOME PHARMACOLOGICAL PROPERTIES OF 4-AMINOPYRIDINE AND 3,4-DIAMINOPYRIDINE IN VIVO

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SUMMARY

4-Aminopyridine and 3,4-diaminopyridine have been compared with respect to their interactions with morphine in the mouse in vivo. In contrast to 4-aminopyridine, 3,4-diaminopyridine was capable of reducing morphine-induced respiratory rate depression in doses which did not produce signs of toxicity.

Both 4-aminopyridine and 3,4-diaminopyridine have been shown to stimulate the central nervous system, increase arterial pressure and antagonize neuromuscular blockade (Thesleff, 1980). 4-Aminopyridine has been used in man to aid the reversal of neuromuscular blockade (Miller et al., 1979) and for reversal of opioid-induced respiratory depression (Sia et al., 1979) and ketamine-diazepam anaesthesia (Agoston et al., 1980). 3,4-Diaminopyridine might be a safer antagonist to neuromuscular blockade as it has greater potency than 4-aminopyridine in this respect (Molgo, Lundh and Thesleff, 1980), but is less convulsant, at least in laboratory animals (Vohra and Pradhan, 1964). The reduced central nervous system toxicity of 3,4-diaminopyridine has been attributed to its relative inability to cross the blood-brain barrier (Lemeignan et al., 1981).

Reversal of opioid-induced respiratory depression by 4-aminopyridine may be a consequence of generalized central nervous system stimulation which is manifest as convulsions with higher doses. On the other hand, it may be a selective effect of this class of drugs. In the present study this possibility has been examined by comparing the ability of 4-aminopyridine and of 3,4-diaminopyridine to reverse morphine-induced respiratory rate depression in the mouse.

METHODS

Morphine antagonism in mice

Groups of 12 mice (Manchester strain) weighing 25-40 g were used. Respiratory rate was measured by placing the snout of the mouse in the barrel of a 5-ml syringe connected to a pressure transducer and Grass 79C polygraph. The respiratory pattern was recorded for 10 s after a steady state had been established, usually within a few seconds. Just after each measurement of respiratory rate, antinociceptive activity was measured using the mouse hot-plate reaction-time test (Woolfe and MacDonald, 1944). The hot-plate was maintained at a temperature of 55 °C ± 1 °C. The reaction time was taken from the time that the mouse made contact with the plate until a sign of discomfort in the hind paws was observed.

The mice were assessed visually for signs of ataxia or convulsions throughout the experiments. Respiratory rate and reaction time were measured just before the injection of drugs and then at 15-min intervals until 90 min after drug injection.

In each experiment the mice received saline plus morphine, saline plus saline, saline plus a dose of an aminopyridine, or morphine plus a dose of an aminopyridine. The doses of drugs used were morphine hydrochloride 20 mg kg⁻¹, 4-aminopyridine 0.4, 0.8 and 1.6 mg kg⁻¹ and 3,4-diaminopyridine 0.1, 0.4 and 0.8 mg kg⁻¹ and all were injected in a volume of 0.1 ml/10 g body weight i.p.

Students' t test or the Mann-Whitney U test was used to assess significant differences between groups, using only concurrently tested mice.

RESULTS

There was no significant difference in respiratory rates between mice receiving saline and those receiving any of the three doses of 4-aminopyridine, although the respiratory rates in both these sets of mice decreased by 5-10% over 90 min. Morphine 20 mg kg⁻¹ induced the expected decrease in respiratory frequency (fig. 1). The addition of 4-aminopyridine reduced the depression caused by morphine but, throughout the time-course of action of morphine, this reached statistical significance.

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FIG. 1. Interaction between 4-aminopyridine 1.6 mg kg⁻¹ and morphine hydrochloride 20 mg kg⁻¹ on respiratory rate (A) and hot-plate reaction time (B) in mice (means ± SEM, n = 12). *P < 0.05 compared with morphine alone. ○ = saline + saline; △ = saline + 4-aminopyridine; = morphine + saline; △ = morphine + 4-aminopyridine.

FIG. 2. Interaction between 3,4-diaminopyridine 0.1 mg kg⁻¹ and morphine hydrochloride 20 mg kg⁻¹ on respiratory rate (A) and hot-plate reaction time (B) in mice (means ± SEM, n = 12). *P < 0.05 compared with morphine alone. ○ = saline + saline; • = saline + 3,4-diaminopyridine; □ = morphine + saline; △ = morphine + 3,4-diaminopyridine.
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only with the 1.6 mg kg\(^{-1}\) dose (fig. 1). At this dose of 4-aminopyridine, more than 40% of the mice were grossly ataxic, and some convulsed.

When given with saline, 3,4-diaminopyridine had no significant effects upon respiratory rate. However, 3,4-aminopyridine reduced the depression of respiratory frequency induced by morphine and this was statistically significant with the 0.1-mg kg\(^{-1}\) dose (fig. 2), 0.4-mg kg\(^{-1}\) and 0.8-mg kg\(^{-1}\) doses of 3,4-diaminopyridine, although even the largest dose did not completely reverse the effects of morphine. Only 8% of mice given the highest dose of 3,4-diaminopyridine exhibited ataxia, and no ataxia was seen in the smaller doses.

Hot-plate reaction time was unaffected by any dose of 4-aminopyridine. Mice given morphine plus 4-aminopyridine tended to have reaction times shorter than mice given morphine alone, but this was rarely significant (fig. 1). Similar observations were obtained for 3,4-diaminopyridine (fig. 2), with the exception of the largest dose (0.8 mg kg\(^{-1}\)), with which morphine-induced antinociceptive activity at 15 min was reduced from 10.81 ± 0.8 s in control animals to 7.3 ± 0.7 s in mice given diaminopyridine.

DISCUSSION

4-Aminopyridine reduced morphine-induced depression of respiratory rate in mice only in those doses which also produced signs of general toxicity, such as ataxia and convulsions. In contrast, 3,4-diaminopyridine reduced morphine-induced respiratory rate depression at a dose one-eighth of that which produced signs of toxicity. Thus 3,4-diaminopyridine has greater selectivity for this action than the 4-amino derivative, at least in the mouse. Neither of the aminopyridines stimulated respiratory rate when given alone in the doses used. This suggests that they may have a selective action on the depressed respiratory centres or, alternatively, a more direct interaction with the activity of morphine. The antinociceptive activity of morphine was unaffected by 4-aminopyridine and the smaller doses of 3,4-diaminopyridine, which may indicate that the antagonism of morphine-induced respiratory rate depression was not a result of a generalized change in the bioavailability of morphine. The reduction of the antinociceptive activity of morphine by the highest dose of 3,4-diaminopyridine is not surprising, as similar findings have been reported for 4-aminopyridine in the experimental animal (Tung and Brandom, 1981).

Preliminary in vivo studies in our laboratory confirmed the findings of Molgo, Lundh and Thesleff (1980) that 3,4-diaminopyridine has six times the potency of 4-aminopyridine as an antagonist of neuromuscular blockade (J. Sinha, personal communication). Thus, 3,4-diaminopyridine warrants further detailed study as it may prove more useful than 4-aminopyridine for routine clinical use.

REFERENCES


COMPARAISON DE QUELQUES PROPRIETES PHARMACOLOGIQUES DE LA 4-AMINOPYRIDINE ET DE LA 3,4-DIAMINOPYRIDINE IN VIVO

RESUME

Nous avons comparé, in vivo chez la souris, les interactions entre la morphine et la 4-aminopyridine d’une part ou la 3,4-diaminopyridine d’autre part. A l’encontre de la 4-aminopyridine, la 3,4-diaminopyridine est capable de réduire la dépression de fréquence respiratoire induite par la morphine, à des doses qui ne provoquent pas de signes de toxicité.
ZUSAMMENFASSUNG

4-Aminopyridin und 3,4-Diaminopyridin wurden bezüglich ihrer Interaktionen mit Morphin in vivo an der Maus verglichen. 3,4-Diaminopyridin konnte im Gegensatz zu 4-Aminopyridin die Morphin-induzierte Depression der Atmungsfrequenz ohne toxische Nebenwirkungen verbessern.

SUMARIO

Se llevaron a cabo comparaciones de la aminopiridina-4 y de la diaminopiridina-3,4 con la morfina en ratones in vivo en lo que se refiere a sus interacciones. Contrariamente a la aminopiridina-4, la diaminopiridina-3,4 pudo reducir la depresión del ritmo respiratorio inducida por la morfina con dosis que no produjeron señales de toxicidad.