Morphine Antagonism with Amiphenazole (2,4-Diamino-5-Phenyl-Thiazole Hydrochloride) (24608)

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Shaw and Shulman(1) and others(2,3,4) report that concurrent administration of amiphenazole with morphine 1) permitted rapid increments in morphine dosage, 2) eliminated signs of development of tolerance or addiction to morphine, and 3) antagonized respiratory depressant effects of morphine. Shaw and Shulman(1) also point out that amiphenazole by itself is nontoxic in therapeutic doses and does not precipitate symptoms of abstinence from morphine in addicted patients. Fraser and co-workers(5) were unable to confirm these effects in man. This report presents data which confirm the report(6) that amiphenazole antagonizes morphine depression in dogs; the data also show that amiphenazole does not significantly affect morphine analgesia in mice.

Methods. Healthy dogs of both sexes were used. Morphine, 10 mg/kg, with hyoscine, 0.6 mg/kg, was given by subcutaeous injection. Usually analgesia sufficient to allow for minor surgical procedures and lasting several hours was obtained; unless severe morphine depression was obtained the animals were not used for testing. The compounds to be tested, amiphenazole and bromosulfolane, (3-bromotetrahydrothiophene-1, 1-dioxide)(7), were administered intravenously (i.v.). Dogs were observed for signs of arousal at least one hour and, if these appeared, they were watched for further period to determine whether depression recurred. The above procedure and the graded end points are those of Shaw and Bentley(6). In dogs anesthetized with pentobarbital sodium, mean blood pressures were recorded with mercury manometer. Amiphenazole was administered rapidly intravenously. *Analgetic activity* was determined in albino male Webster-Swiss mice by thermal method described by Chen and Beckman(8). Controls were run simultaneously each time that drugs were evaluated; all compounds were administered intraperitoneally (i.p.) to 10 mice at each dose level.

Results. In 4 anesthetized dogs, amiphenazole, 20 mg/kg caused average transient (less than 10 minutes) lowering of mean blood pressure of 47% (range 35 to 70). Atropinization (3 dogs) failed to alter this vasodepression (53%, range 37 to 75%).

Amiphenazole was more effective than bromosulfolane in counteracting morphine depression in dogs without inducing disturbing side effects. In 5 of 12 dogs the antagonism was outstanding: only 2 dogs failed to respond satisfactorily. Bromosulfolane was inactive in 4 dogs and showed good arousal in 2. Although amiphenazole is a central nervous system (CNS) stimulant, the dose of 20 mg/kg produced no signs other than respiratory stimulation in dogs depressed with morphine or in normal control dogs. This contrasts with results found in rats(9). On the other hand, bromosulfolane consistently produced bothersome CNS stimulant effects. Following amiphenazole about half of the dogs returned in ½ to 4 hours to a level of morphine depression somewhat less than that observed before drug. The results were not as consistent as those previously reported by Shaw and Bentley(6). In 15 dogs these investigators had good arousal in 12, mild arousal in 3, and no failures.

Amiphenazole, 100 mg/kg i.p. in mice, produced hyperexcitability, shaking, and ataxia following which the animals became quiet. At higher dosages, opisthotonos, threshold and clonic convulsions, loss of righting reflex, and salivation were observed. This was usually followed by moderate post-ictal depression, which is not uncommon for CNS stimulants.

Amiphenazole did not significantly alter the analgetic effects of morphine in mice (Fig. 1). Mice receiving combinations of morphine plus amiphenazole at 40 and 80 mg/kg were withdrawn and quiet, but not ataxic, at first 30

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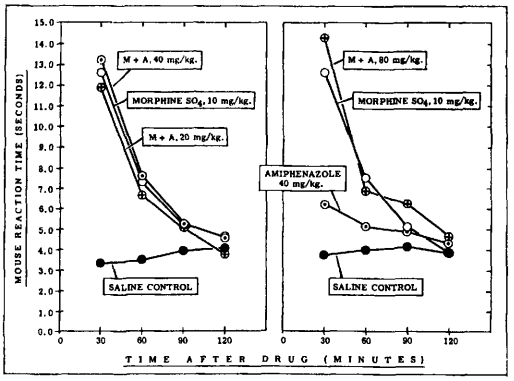

FIG. 1. Analgetic activity of morphine SO_4, amiphenazole and combinations of morphine SO_4, 10 mg/kg with various amounts of amiphenazole (M + A). All reaction times greater than 5.5 seconds were significantly greater ($P < .05$) than control. Each half of Figure represents independent experiment.

minute interval. This depression was not seen with morphine alone or with amiphenazole alone at 40 mg/kg. An unexpected and unexplained finding was that amiphenazole, 40 mg/kg, produced a significant ($P < .01$) analgetic effect itself at 30 minutes.

Summary. Amiphenazole was effective in antagonizing morphine depression in dogs; bromosulfolane was less effective even at toxic doses. Amiphenazole did not significantly alter the analgetic effect of morphine in mice, though this compound alone produced a mild but transient analgetic effect.

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Fibrinolysis II: Absence of Antibodies to Streptokinase Following Injection of Purified Human Plasmin in Rabbits.* (24609)

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Human plasmin (fibrinolysin) may be useful in control of thromboembolism. Thus it becomes important to establish its antigenic properties, since these could limit greatly its clinical use. This paper discusses the heteroantibody response in rabbits receiving purified human plasmin. Special reference is made to development of antibodies against streptokinase.

Materials and methods. (a) *Streptokinase,* a highly purified preparation, supplied by Dr. James Ruegsegger,‡ was stated to induce specific antigenic response when given intramuscularly to rabbits (Ablondi, personal communication). (b) *Preparation of human plasminogen (profibrinolysin).* Pooled citrated platelet-poor normal human plasma was stored at −20°C until used. After slow thawing in ice box, Fractions II and III of plasma were prepared by Cohn's method #6(1) (protein yield 1.8%), and Fraction III then obtained by

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