Alterations in the Absorption of Sulfisoxazole from Guinea Pig Intestine

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The effect of neostigmine on the absorption of sulfisoxazole into everted sacs of guinea pig intestine was determined and the results related to the blood levels of the sulfonamide after oral administration. The results indicate that neostigmine enhanced the absorption, thereby elevating the total blood level of sulfonamide.

POTENTIATION (1–3) of activity and increased concentration (4, 5) of drugs have been reported in animals pretreated with cholinesterase inhibitors. This study was initiated to ascertain if neostigmine could increase the transfer of sulfonamide across the intestinal membranes and increase the blood concentration in a given interval.

Sulfisoxazole was determined colorimetrically using an adaptation of the Hoffmann-LaRoche assay for sulfadimethoxine.[1] The standard curve was obtained using U.S.P. reference standard sulfisoxazole.

EXPERIMENTAL

Determination of the Absorption into Everted Sacs.—Guinea pigs weighing between 300 and 400 Gm. were selected at random; everted sacs of approximately 15 cm. were prepared from the small intestine after the technique of Wilson and Wiseman (6).

There were two groups of eight sacs each used in the experiment. The two groups were divided in a manner so that each group contained the same number of sacs made from the lower portion of the small intestine. (Better absorption from this portion of the small intestine was noted in guinea pigs.) The sacs of group *A* were filled with 10 ml. of balanced salt solution [Sollmann-Rademaeker (7) solution, pH 8]. Group *B* was filled with the same salt solution plus neostigmine (0.02 mcg./ml.). An oxygen bubble was added to each sac; the sacs were immersed in a tissue bath and maintained at 37°. The tissue bath for group *A* contained balanced salt solution plus sulfisoxazole (5 mcg./ml.), while group *B* was suspended in balanced salt solution plus sulfisoxazole (5 mcg./ml.) and neostigmine (0.02 mcg./ml.). All sacs were removed after 15 minutes and 5 ml. of solution aspirated from each for the sulfonamide assay.

The mean concentration of sulfonamide inside everted sacs with sulfonamide alone was 0.327 mcg./ml. (range 0.25 to 0.50), while that in sacs with neostigmine added was 1.78 mcg./ml. (range 1.20 to 2.60) (Fig. 1). All sacs showed an increase of approximately 10% in fluid volume.

Determination of Blood Levels 4 Hours After 400 mg./Kg. of Sulfisoxazole Orally.—Fifteen guinea pigs weighing between 325 and 425 Gm. and selected at random were used in this study. Six pigs were administered sulfisoxazole (400 mg./Kg.) orally as sulfisoxazole diethanolamine injection diluted to a total volume of 5 ml. Nine pigs were treated likewise, except that neostigmine (0.2 mcg./Kg.) was added to the oral medication. The animals were returned to the cage and allowed food and water. After 4 hours, 6 ml. of blood was removed by cardiac puncture and the total sulfonamide determined. The mean blood level of animals administered sulfonamide alone was 9.72 mcg./ml., with a range from 6.9 to 11.5 mcg./ml. Neostigmine plus sulfisoxazole treated animals showed a mean blood level of 12.76 mcg./ml., with a range from 12.1 to 14.5 mcg./ml. (Fig. 2).

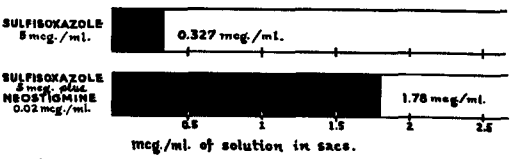

Fig. 1.—Sulfisoxazole 15-minute absorption from everted sacs of guinea pig intestine. [Sollmann-Rademaeker bathing solution (7).]

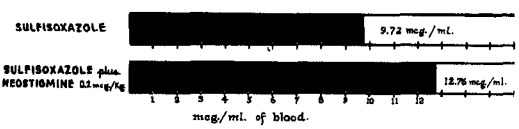

Fig. 2.—Blood levels 4 hours after sulfisoxazole (400 mg./Kg.) orally in guinea pigs.

DISCUSSION AND CONCLUSIONS

Neostigmine increased the sulfisoxazole transfer from the mucosal to the serosal surface of the guinea pig intestine. It also increased the 4-hour blood level of the same sulfonamide after oral administration.

The author and other investigators have reported that certain cholinesterase inhibitors, including neostigmine, increase tissue uptake of certain chemicals and decrease the uptake of others. It would appear from this study that these reported observations are based on the ability of cholinesterase inhibitors to change tissue permeability. Because these inhibitors, observed as having such activity, are so different chemically and have exhibited different modes of activity, it appears that their influence on permeability is linked to their common anticholinesterase activity.

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[1] Marketed as Madribon by Hoffmann-LaRoche, Inc.