vascular relations may also have been involved. Obviously, these possibilities are as yet conjectural.

10895

Sulfapyridine Potentiation of Narcotic and Toxic Effects of Papaverine* in Rats and Rabbits.

SUSI GLAUBACH. (Introduced by W. Antopol.)

From the Laboratories of the Newark Beth Israel Hospital, Newark, N. J.

In the course of investigating the effect of papaverine on the blood pressure of rabbits treated with sulfapyridine,‡ [1] it was observed that, in these animals, papaverine had a profound narcotic effect. This finding is significant since the literature refers only to the sedative action of papaverine, Schroeder[2] reported that the oral administration of 0.5 g of papaverine produced drowsiness only, and that 1.0 g produced sleep and catatonia in ¼ to ½ hour. Deep narcosis was not observed even with 2.0 g, and increased excitability, rather than sedation, ensued. This was evidenced by shivering, convulsions, dyspnoea, dilation of the pupils and finally arrest of respiration and death. Similar findings were obtained by Zeelen[3] after the subcutaneous injections of papaverine in normal rabbits. He also was unable to produce deep narcosis.

The present investigation deals with the effect of papaverine on rabbits and rats to which sulfapyridine had been previously administered. The animals were first tested for their reaction to papaverine alone. After a rest period of 6-8 days the papaverine was injected subcutaneously 3 hours after the oral administration of sulfapyridine. Eight to 10 days later the animals which survived the second set of experiments were again retested for the papaverine response alone.

Rat Experiments. In this series 10 male rats weighing between 120-200 g were used. All of the animals received a subcutaneous injection of 0.3 mg papaverine per gram of rat. Sedation, diminished

* The term papaverine is used to designate Papaverine Hydrochloride.

‡ We wish to thank Dr. J. J. Carlisle of Merck & Co. for supplying the sulfapyridine used in this investigation and to express our appreciation to Miss Bessie Zirin for her technical assistance.

1 Work in progress in collaboration with W. Antopol.

2 v. Schroeder, A., *Arch. f. exp. Path.*, 1883, **30**, 125.

3 Zeelen, B., *Z. f. exp. Path. u. Ther.*, 1911, **8**, 590.

tonus of the muscles of the hind limbs, and catatonia were observed in 15-20 minutes in 7 of the animals. These effects lasted for about 1 hour and then rapidly disappeared. The remaining 3 rats showed no detectable nervous effect. Six days later the animals were fed 4 mg sulfapyridine per gram body weight, followed in 3 hours by 0.3 mg papaverine per gram body weight subcutaneously. The exaggeration of the papaverine effect was striking. In 5-15 minutes all the rats were in deep anesthesia. In 3 rats, the narcotic effect was interrupted by brief convulsions. Six of the animals died in 15 to 36 minutes. In these, breathing was first accelerated, then shallow, later irregular, and finally ceased while the heart continued to beat. If artificial respiration was administered, the heart beat could be maintained for 10-15 minutes, after which it became weak and slow, and finally ceased. At necropsy, the heart was found to have stopped in diastole.

The 4 surviving rats recovered from the deep narcosis in 3-4 hours. Ten days later these animals were again tested for papaverine effect alone, at which time they showed no observable nervous manifestations whatsoever.

Rabbit Experiments. These experiments were similar to those performed on the rats. Nine rabbits weighing 1600-2000 g were used. Seven of these received a subcutaneous injection of 0.15 g, one 0.2 g, and one 0.04 g papaverine per kilo body weight. The representative effects are exemplified in rabbit No. 1603. After sulfapyridine, the papaverine acted not only more profoundly, but also started earlier and lasted longer than with papaverine alone in the initial experiment. Eight days later the experiment was again repeated with the sulfapyridine and papaverine, with identical results. After a rest of 8 more days, papaverine alone again was employed, without any recognizable nervous manifestations. Since it is reported that the effect of papaverine is diminished after repeated administration, it is likely that here also the absence of papaverine effect when administered alone in the final phase of the experiment was also dependent upon an increased tolerance to it. To substantiate this, after another rest period papaverine was again administered with sulfapyridine and a repetition of its profound toxic effect and death of the animal resulted.

In the other 8 rabbits, there was also a pronounced potentiation of the papaverine effect when it was administered after the sulfapyridine. Three rabbits died when the papaverine was given after the sulfapyridine. After 8 days the surviving 5 rabbits were tested with the papaverine alone and showed slight or no effect.

The animal which received 0.04 mg papaverine per kilo body weight, a dose which produces no demonstrable nervous effect, also showed a definite papaverine effect when administered after sulfapyridine.

It remained to be determined whether papaverine, due to its dilating effect on the splanchnic vessels, caused concomitant increase in sulfapyridine absorption, thus giving the added effect, or whether the central nervous system was sensitized for papaverine by the sulfapyridine. With sulfapyridine in non-fatal doses no nervous symptoms have been observed,[4] in contrast to sulfanilamide which produces ataxia and intoxication.[5–8] Sulfapyridine determinations were made in the blood after administration but before papaverine injection, at the height of the narcosis after papaverine, during recovery, and when the animal appeared normal. The total sulfapyridine was found to be higher during the phase of recovery than during the narcosis, and even when the animal appeared to have recovered completely, the total sulfapyridine in the blood was 75% higher than at the height of the narcosis. It may be concluded, therefore, that the sulfapyridine appeared to have a latent effect which was only detectable after papaverine was administered and that the deep anesthetic effects were not dependent upon increased blood sulfapyridine.

This finding may be of importance in cases in which patients receive alkaloids which affect the nervous system. Investigations with codeine, morphine, soporifics and analgesics as well as similar studies with sulfanilamide are now under investigation.

It is interesting to note that apparently more sulfapyridine becomes esterified under the effect of papaverine. This may be of interest in view of the finding of acetylated sulfapyridine urolithiasis in animals [9] The influence of various medications on the esterification of sulfapyridine also is being investigated.

Summary. 1. Sulfapyridine potentiates the anesthetic action of papaverine. 2. This is not dependent upon an increased concentration of sulfapyridine in the blood.

---

4 Molitor, H., and Robinson, H., *J. Pharm. and Exp. Therap.*, in press.

5 Halpern, B. N., and Meyer, R. L., *Presse Med.*, 1937, **45**, 747.

6 Marshall, E. K., Jr., Cutting, W. C., and Emerson, K., Jr., *J. A. M. A.*, 1938, **110**, 252.

7 Wien, R., *Quart. J. Pharm.*, 1938, **11**, 217.

8 Molitor, H., and Robinson, H., *J. Pharm. and Exp. Therap.*, 1939, **65**, 405.

9 Antopol, W., and Robinson, H., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 428.