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Abstract

1. Sinomenine and Irgapyrin, the two antirheumatics known to be capable of releasing histamine, caused a marked gastric secretion in the unanesthetized dog. 2. The facial edema and itching associated with histamine release by sinomenine was almost completely eliminated by NeoAntergan, but the gastric secretion was not suppressed, or rather increased - an observation also reported by Paton and Schachter with Compound 48/80. This indicates that the histamine release cannot be markedly prevented by antihistamine agents in this animal. 3. The gastric secretion induced by Irgapyrin was not suppressed by Neo-Antergan but Irgapyrin originally never caused other symptoms associated with histamine release. This is probably due to the antihistamine action inherent in this compound itself. 4. No such histamine-releasing activity, as determined by gastric secretion, could be observed in aminopyrine or butazolidine sodium, the components of Irgapyrin. 5. Sinomenine, differing from Irgapyrin and Compound 48/80, was ineffective by intramuscular injection.

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THE EFFECT OF AN ANTIHISTAMINE AGENT ON THE GASTRIC SECRETION INDUCED BY SINOMENINE AND IRGAPYRIN[1]

By

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Paton and *Schachter* (1951) observed that a histamine-releasing substance, Compound 48/80, caused secretion of a large amount of gastric juice in the unanesthetized dog. They showed that symptoms associated with histamine release, such as facial swelling and itching, were almost completely eliminated by mepyramine, but the amount of histamine liberated, as determined by the amount of gastric secretion, was not reduced.

In recent times, the histamine-releasing action of sinomenine (*Mayeda*, 1953, 1954) and Irgapyrin (*Yamasaki* et al., 1955; *Kumé*) was found in this laboratory, but not that of aminopyrine and butazolidine sodium (*Kumé*). However, no studies have yet been made on the effect of these drugs on the gastric secretion. More recently, *Tasaka* (1956) observed that the rate of histamine release from the minced skin of a dog induced by sinomenine and anaphylatoxin was markedly reduced by Benadryl and Neo-Antergan (mepyramine) in a dilute concentration. This latter finding does not agree with that of *Paton* and *Schachter*.

The present series of experiments were undertaken in order to observe the action of these antirheumatics on gastric secretion and the effect of Neo-Antergan on such action, examined in unanesthetized dogs according to the technique of *Paton* and *Schachter*.

Methods

Female dogs of 9—11 kg. weight were equipped with a

1) Preliminary abstract in Folia pharmacol. japon. **52**, 81 § (1956)

gastric cannula made of nickel-plated brass. Cannula was stoppered when not in use. These dogs had been trained to stand quietly for a certain length of time supported by a few bands in a frame for the collection of gastric juice. Under such a condition, secretion of gastric juice was very small, being less than 5 cc. per hour at the most, and the juice was very low in acidity or even alkaline. There were no indications of bile regurgitation during all the experiments. The gastric juice, collected every 15 minutes and filtered, was titrated for total hydrochloric acid with phenolphthalein as the indicator.

The thickness of the cheeks of these dogs was measured with a micrometer, lightly loaded with a suitable spring, at 2 cm. above the corner of the mouth. The measurement was shown by the mean value of the readings, but the difference never exceeded 0.2 mm.

Histamine dihydrochloride, sinomenine hydrochloride[2], and Irgapyrin, and in some experiments, aminopyrine, butazolidine sodium, and Compound 48/80[3], were administered by subcutaneous injection. In case Neo-Antergan was used at the same time, it was injected subcutaneously 15 minutes prior to the administration of other drugs.

Results

Subcutaneous injection of 15 mg. of sinomenine hydrochloride caused severe signs of itching, facial swelling, and marked secretion of gastric juice, as reported by *Paton* and *Schachter* with Compound 48/80. Pruritus was learned from the movement of the dog, such as licking of the upper lip and the nose and rubbing the face against the frame, and this was the first symptom that appeared. Facial swelling was marked around the mouth, eyelids, and ear-flaps, and accompanied with erythema in these area and areola of the nipples. Secretion of gastric juice began 5—10 minutes after the injection, showed the maximum in the second 15-minute period, and continued for one and half hours or more (Fig. 1). This gastric response was

2) Supplied through the courtesy of the Shionogi Research Laboratories, Imafuku 192, Amagasaki.

3) Kindly supplied by Dr. *Edwin J. de Beer*, the Welcome Research Laboratories, Tuckahoe 7, New York.

approximately comparable to that to 10 mg. of Compound 48/80 used by *Paton* and *Schachter*.

Table 1. Gastric secretion produced by sinomenine with and without Neo-Antergan

In all experiments sinomenine hydrochloride 15 mg. was given subcutaneously. Italic figures refer to experiments in which Neo-Antergan was injected subcutaneously 15 minutes before sinomenine. Neo-Antergan dosis: 2 mg./kg. in no. 2 and 3; 5 mg/.kg. in no. 1 and 4.

Dog (Serial no.)	cc. 0.1 N-HCl secreted on days: 1	6	11	16	Ratio of secretion after sinomenine + Neo-Antergan to secretion after sinomenine alone
1	*82.8*	41.8	44.8	*87.8*	1.97
2	53.3	*56.7*	*67.4*	27.0	1.55
3	*76.3*	39.4	37.9	*68.5*	1.87
4	26.3	*25.3*	*36.8*	12.1	1.62
Total	238.7	163.2	186.9	195.4	Av. 1.75

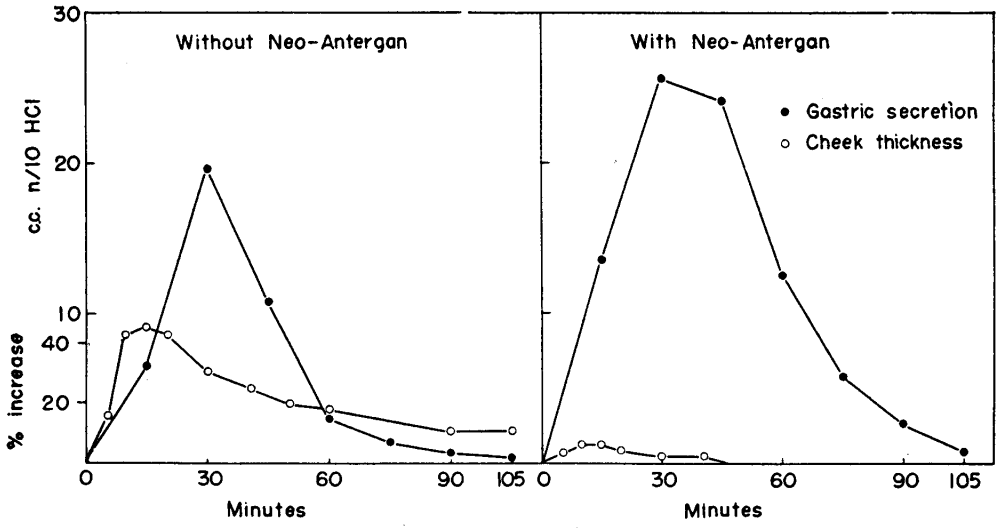

Fig. 1. Gastric secretion in cc. 0.1 N-HCl per 15-minute sample and per cent increase in cheek thickness, produced by sinomenine hydrochloride 15 mg. subcutaneously at zero time (left) and by the same injection of sinomenine with Neo-Antergan 5 mg./kg. subcutaneously 15 minutes previously (right). Each is the average of two cross-over tests. Dog. no. 1.

After subcutaneous injection of 2 or 5 mg./kg. of Neo-

Antergan sinomenine caused no apparent signs of pruritus, swelling, or erythema, although the gastric secretion was not suppressed but rather increased (Fig. 1 and Table 1). In the dose used, Neo-Antergan itself did not affect gastric secretion.

The gastric secretion induced by sinomenine developed a temporary state of complete refractoriness when the injection was repeated at a short interval but even under such conditions, the response to histamine did not decrease so markedly. When the interval of injection was prolonged to over 2—3 days, the responsiveness to sinomenine returned, though insufficiently. This phenomenon may be explained by the fact that the depleted tissue histamine takes a long time to recover (*Feldberg* and *Talesnik*, 1953).

Gastric secretion comparable to that induced by the foregoing dose of sinomenine was caused by 0.5 mg. of histamine.

Table 2. Gastric secretion produced by histamine with and without Neo-Antergan

In all experiments histamine dihydrochloride 0.5 mg. subcutaneously. Italic figures refer to experiments in which Neo-Antergan was given subcutaneously 15 minutes before histamine. Neo-Antergan dosis: 2 mg./kg. in no. 6 and 7; 5 mg./kg. in no. 5 aud 8.

Dog (Serial no.)	cc. 0.1 N-HCl secreted on days: 1	4	7	10	Ratio of secretion after histamine + Neo-Antergan to secretion after histamine alone
5	73.8	*66.8*	*86.0*	50.3	1.23
6	*56.1*	39.1	48.1	*44.3*	1.15
7	42.4	*47.5*	*41.6*	31.3	1.21
8	*40.9*	39.6	36.4	*40.1*	1.07
Total	211.1	193.0	212.1	162.9	Av. 1.17

However, facial edema was externally indistinct and precise measurement showed less than 10% increase in the thickness of the cheek. Signs of itching were entirely absent. Neo-Antergan was also able to cancel even the slight swelling of the cheek elicited by histamine but increased the gastric secretion by histamine in all the cases, though in a very slight degree (Table 2). Reduction of the response of gastric secretion by repeated injections of histamine was slight and the responsiveness was restored

Table 3. Gastric secretion produced by Irgapyrin with and without Neo-Antergan

Irgapyrin 100 mg./kg. subcutaneously. Italic figures refer to experiments in which Neo-Antergan was injected subcutaneously 15 minutes before Irgapyrin. Neo-Antergan dosis: 2 mg./kg. in no. 10; 5 mg./kg. in no. 9.

Dog (Serial no.)	cc. 0.1 N-HCl secreted on days: 1	5	9	13	Ratio of secretion after Irgapyrin + Neo-Antergan to secretion after Irgapyrin alone
9	31.3	*29.7*	*32.7*	29.3	1.03
10	*47.5*	47.7	49.8	*46.5*	0.96
Total	78.8	77.4	82.5	75.8	Av. 1.00

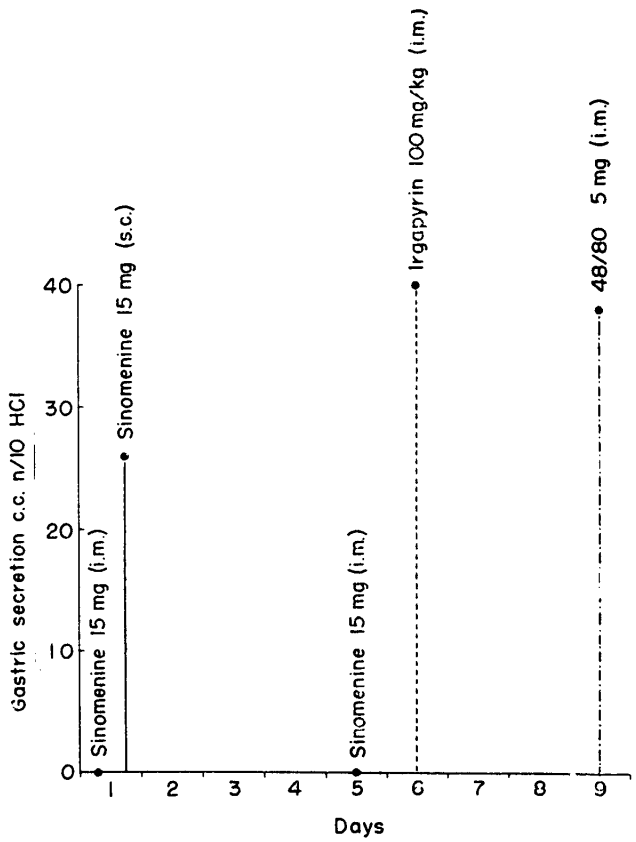

Fig. 2. Gastric secretory responses in total cc. 0.1 N-HCl to intramuscularly injected sinomenine, Irgapyrin and Compound 48/80. Inability of intramuscularly injected sinomenine is contrasted with a distinct effect of subcutaneous injection of the same dose.

completely by the following day.

Subcutaneous injection of 100 mg./kg. of Irgapyrin produced gastric secretion comparable to that produced by the foregoing two drugs. In this case, facial swelling was not observed at all, even by precise measurement, and both reddening and itching were entirely absent. The response of gastric secretion to Irgapyrin was not increased or decreased by Neo-Antergan, differing from the cases of sinomenine and histamine (Table 3). However, repetition of its injection developed a fair degree of refractoriness. Neither aminopyrine nor butazolidine sodium caused gastric secretion or any other signs associated with histamine release, when used individually in 100 mg./kg. dose.

In his clinical experience, *Mannami* (1955) observed that the intramuscular injection of sinomenine failed to cause side effects, such as facial edema and itching, which appear by its subcutaneous injection. The present author also observed that the intramuscular injection of sinomenine strangely did not cause gastric secretion or any other signs usually seen after its subcutaneous injection. However, both Compound 48/80 and Irgapyrin were effective by this route as by subcutaneous injection (Fig. 2).

Discussion

The results observed with sinomenine are practically the same as those reported for Compound 48/80 by *Paton* and *Schachter* (1951), except for the earlier start of gastric secretion induced by the former drug after the injection. Such similarity of these snbstances may be understood by the fact that sinomenine shows pharmacological actions similar to Compound 48/80 as a specific histamine releaser (*Mayeda*, 1953; *Yamasaki* et al. 1955). Neo-Antergan markedly eliminated the signs and symptoms elicited by either of the injected or liberated histamine, but did not suppress gastric secretion induced by histamine. This indicates that the antihistamine is not capable of preventing the histamine release of sinomenine and suggests that the suppression of histamine release by antihistamines may not be as marked in vivo as in in vitro experiments (*Tasaka*, 1956).

The increase of gastric secretion induced by sinomenine by the concurrent use of Neo-Antergan may be explained by the assumption made by *Paton* and *Schachter* that the edema of gastric mucosa, which is known to reduce gastric secretion (*Ricketts*, *Kirsner* and *Palmer*, 1949), occurs together with facial swelling and this is eliminated by the antihistamine. In the present series of experiments, Neo-Antergan seemed to give slight but similar effect even in the case of histamine.

Irgapyrin was found to induce gastric secretion but it is interesting that neither of its components, aminopyrine or butazolidine sodium, possessed such action individually. *Yamasaki*, *Kamimura* and *Tasaka* (1954), in their experiments on in vitro histamine release using minced tissues of guinea pig lungs and dog skin, found this action only in Irgapyrin among these three drugs. More recently, *Kumé* also proved the same relation of these drugs in the effect of depleting skin histamine of the unanesthetized dog by subcutaneous injections. It seems reasonable, therefore, to assume that gastric secretion induced by Irgapyrin is produced by histamine release. However, this compound showed no other indications of histamine release, such as facial swelling and itching. Such facts may also explain the reason why Neo-Antergan had no influence on the gastric secretion induced by Irgapyrin, differing from the case of sinomenine and Compound 48/80, because the edematous swelling of gastric mucous membrane is not likely to be induced by Irgapyrin.

The foregoing facts also present the possibility that the marked gastric secretion induced by Irgapyrin may occur chiefly by some mechanisms other than histamine release. But, *Kumé* observed that the subcutaneous injection of five doses of 20 mg./kg. of Irgapyrin caused a reduction of skin histamine in a dog, approximating that similarly caused by five 3 mg./kg. of sinomenine. The amount of histamine released by 100 mg./kg. of Irgapyrin may be sufficient to cause gastric secretion. Another possibility is that Irgapyrin itself possesses an antihistaminic action as well as a histamine-releasing action. If this is the case, facial signs due to histamine release will not appear and its gastric secretion will not be affected by Neo-Antergan. This supposition is supported by the experimental result of

Wilhelmi (1949) who demonstrated that Irgapyrin increased the lethal dose of histamine in a guinea pig and alleviated the spastic contraction of guinea-pig intestines and rabbit aural vessels caused by histamine.

It would be interesting to imagine that the excellent clinical effect of Irgapyrin, compared to its components, is due to the concurrent histamine-releasing action, because sinomenine, which is a specific histamine liberator, also possesses an antirheumatic effect (Ishiwari, 1921; Takaori, 1921). Investigations on this point is now in progress in this laboratory. In any case, the fact that these drugs clinically used so frequently induce gastric secretion should be kept well in mind, especially in the case of peptic ulcer.

The reason of inability of the intramuscularly injected sinomenine to induce gastric secretion is still obscure at the present. Whether or not sinomenine reacts with muscular tissue components, forming a complex that is not absorbed easily, or losing its activity, is of interest for further studies.

Summary

1. Sinomenine and Irgapyrin, the two antirheumatics known to be capable of releasing histamine, caused a marked gastric secretion in the unanesthetized dog.

2. The facial edema and itching associated with histamine release by sinomenine was almost completely eliminated by Neo-Antergan, but the gastric secretion was not suppressed, or rather increased — an observation also reported by *Paton* and *Schachter* with Compound 48/80. This indicates that the histamine release cannot be markedly prevented by antihistamine agents in this animal.

3. The gastric secretion induced by Irgapyrin was not suppressed by Neo-Antergan but Irgapyrin originally never caused other symptoms associated with histamine release. This is probably due to the antihistamine action inherent in this compound itself.

4. No such histamine-releasing activity, as determined by gastric secretion, could be observed in aminopyrine or butazoli dine sodium, the components of Irgapyrin.

5. Sinomenine, differing from Irgapyrin and Compound 48/80, was ineffective by intramuscular injection.

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