NEW CONCEPTS OF MORPHINE ANALGESIA *

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MORPHINE is still the drug of choice in the alleviation of pain but, exclusive of tolerance and addiction, about which we know very little, it still has important disadvantages with which we are all familiar. It seems reasonable to suppose that many of the drawbacks attending the use of morphine might be reduced if smaller doses could be utilized, provided such doses would effectively relieve pain. All the work which we have done has been directed toward this problem: i.e., of reducing the dose of morphine but still maintaining effective analgesic activity.

With these facts in mind, I should like to present a background for our results regarding morphine analgesia as altered by prostigmine. Several years ago I read an abstract by a Belgian worker, LaBarre (1). He reported that the effects of morphine on the isolated intestine of the rabbit were reinforced by the addition of choline. He further stated that if a strip of isolated rabbit's intestine was decholinized by repeated washings, the action of morphine, as noted on a normal strip, was markedly decreased or was entirely lacking. About this time, one of my colleagues and I had been discussing the curious fact that many of the peripheral actions of morphine were similar to those known to be characteristic of cholinergic drugs.

For our first experiments, we made use of unanesthetized dogs which had been prepared with Thiery-Vella fistulas, so that intestinal contractions could conveniently be recorded. We (2) noted that a combination of a dose of eserine and of morphine, which had no action on the intestine when given separately, produced a reaction on the intestine which simulated the effects of an active dose of morphine alone. There were two differences: (1) peristaltic activity was not reduced as greatly as when an active dose of morphine alone was administered, and (2) the effects did not last as long. The former finding is of clinical importance. The short duration of action was undoubtedly due to the fact that very small doses of each of the drugs were used. Such an effect was clearly a sign of potentiation, since neither of the drugs in the doses used had any effect when given separately.

To ascertain if this peripheral potentiating effect was to be found only when eserine was used, prostigmine, a synthetic drug, was tried in

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relation to the effects of morphine on the stomach activity of unanesthetized dogs. It was found (3) that potentiation also existed between prostigmine and morphine. There was a practical reason as well for the substitution of prostigmine for eserine. We hoped that it would be useful clinically in the relief from pain when combined with morphine —we likewise knew that it was a safe drug to use if proper doses were administered (4, 5).

While we were engaged in these experiments Winter (6) reported enhancement by prostigmine of the action of morphine on bladder function in unanesthetized dogs. Recently, McCrea et al. (7) have shown a similar synergism as regards the effects of prostigmine on morphine miosis. Finally, in our laboratory (8), we have found that prostigmine augments the action of morphine on the isolated ureter. These reports were a "far cry" from the analgesic activity which morphine possesses, but did bear out previous contentions concerning the peripheral actions of morphine.

Our next field of endeavor took up the consideration of analgesia. As in most experimental work, however, animals were first used. In these experiments, the method of Eddy (9) was found to be very useful. By this method, pain was produced in cats by applying pressure to the terminal two inches of the tail. The apparatus is so constructed that the pressure applied can be measured with an error of 0.5 Kg. (Pressures range from 0–22 Kg.) Such a method is comparatively quantitative. Briefly, our results (10) were as follows: The administration of 0.5 mg. per kilogram of morphine plus 0.085 mg. per kilogram of prostigmine produced as good relief from the pressure-pain induced in these animals as did 1 mg. per kilogram of morphine alone. One interesting side observation in these experiments was that with the cited combination of morphine and prostigmine, the cats were much more quiet than they were with 0.5 mg. per kilogram of morphine. Since we showed that prostigmine enhanced the analgesic effects of morphine in the cat, further experiments were done to determine what effect atropine might have on the pain-relief activity of morphine. We found that atropine reduced the analgesic activity of 0.5 mg. per kilogram of morphine by 13 per cent. Further, when a combination of atropine, prostigmine, and morphine was given in doses of 0.04, 0.085 and 0.5 mg., respectively, per kilogram there also was a decreased analgesic response to morphine to the extent of 33 per cent as compared with 0.5 mg./Kg. of prostigmine plus 0.5 mg./Kg. of morphine.

Results so far, then, indicate that morphine acts very much like a cholinergic drug both peripherally and in its effects on pain. In other words, it has been shown that its actions are enhanced by cholinergic drugs and that its activity is reduced by an anticholinergic drug.

Another link in the chain of evidence to support this contention was the work of Bernheim and Bernheim (11). They pointed out that morphine markedly depressed brain choline esterase. Shortly after

their report, we (12) were able to show that morphine lowered the serum choline esterase content of the dog. More recently, Wright (13) has reported a similar activity for morphine as regards its *in vitro* effects on the choline esterase of blood serum.

In this connection Williams (14) has reported some interesting studies on the effect of morphine and choline esterase in human addicts and in post addicts. His chief finding indicated that persons during withdrawal exhibit less choline esterase activity than normal. In a group of post addicts he was unable to observe a reduction in choline esterase values after an injection of morphine. It is not unlikely that post addicts may have their enzyme systems irreversibly altered by reason of their previous addiction.

In our experiments with dogs, the peak of the depression of choline esterase was observed twenty minutes after the morphine had been given. Williams made his determinations on post addicts thirty to forty-five minutes following the injection of morphine. Because of this discrepancy between our findings and the report of Williams, further experiments are indicated.

Our experimental studies to date suggest that morphine fulfills most of the important requirements of a cholinergic drug. We were also interested in excretion studies of morphine as influenced by the coincidental administration of prostigmine. Our results (15) show that there is a reduction of the total percentage of injected morphine which is excreted when prostigmine is administered simultaneously as compared to an equivalent dose of morphine administered separately. The amount of the decreased excretion was about the same in both animals accustomed and non-accustomed to the drug. However, when the reduction of morphine excreted is broken down into component parts, we found that in the non-accustomed animals this relative decrease is reflected almost two to one in the combined as compared with the free form of morphine.

It is only because of the work of Gross and Thompson (16) that we are now able to recover these two forms of morphine. Gross (17) has suggested that the combined morphine excreted may be responsible for analgesia. If one accepts this hypothesis, the retention of morphine in the body as mirrored by the reduction of the urinary output of the combined form of morphine might explain in part the potentiation of morphine analgesia by prostigmine. The recent publication by Himmelsbach et al. (18) indicates that in the human this distinct reduction-relationship does not exist. So far as I know, however, no work was done on non-addict human subjects. These experiments, as those of choline esterase values in the human, need clarification.

Having raised a background from the experimental angle, we felt that it was pertinent to make certain clinical observations (19) using combinations of prostigmine and morphine. Persons who came to the clinic in two large indigent hospitals, and who required an opiate, were

chosen at random. In a few instances we were able to make these patients their own controls; i.e., the effects of 16 mg. of morphine on pain relief were compared with those of 8 mg. plus prostigmine. The important differences between the effects of the combination dose as compared with the larger dose of morphine alone are two: (1) the analgesic action comes on more quickly and (2) lasts longer.

Himmelsbach et al. (18) suggest that our work is perhaps not conclusive because we did not establish whether 8 mg. of morphine was ineffective when given alone. Referring to a paper by Lee, Himmelsbach further states that "8 to 10 mg. morphine *provides adequate* clinical analgesia." From Lee's publications (20, 21) it appears obvious that although he is of the general opinion that clinically too large doses of morphine are sometimes administered, he nevertheless is not as dogmatic as Himmelsbach (18) indicated. In one of his articles he says, "10 mg. of morphine . . . *usually* results in good relief of pain. . . ." In another, he states, ". . . 10 mg. are necessary to insure *fairly adequate relief* in the case." No one will deny that it is extremely difficult to obtain quantitative clinical data on the effects of analgesics by recorded observations. However, we do feel that our observations (19), although limited in number, offer support for our contention that morphine analgesia is potentiated by prostigmine. In support of this view, the clinical observations made independently by Maxfield (22) are cited. He used the combination of 8 mg. of morphine and 0.5 mg. of prostigmine to control pain in persons suffering from neoplastic disease. His conclusions are: "I do believe, without question, that the use of prostigmine and morphine combination is far superior to any other drug combination . . . the well-being and general physical condition of the patient can be better maintained by the use of this combination of drugs than it can by the use of narcotics in any other form." Our hypothesis has been further substantiated by quantitative experiments done on humans. These will be discussed later.

We next used the combination of prostigmine and morphine in obstetrics (23). In these experiments, morphine or morphine-prostigmine was administered as needed to keep the patient completely asleep between pains. Under this regime, it seems incredible that there can be any doubt that the results are indicative of potentiation. In other words, in these obstetrical cases, control groups which might have received 8 mg. of morphine would have added little information since the entire technic was so carried out that the patient was maintained at a predetermined level with regards to discomfort. The results are clear-cut. They show that the combination of morphine-prostigmine is as satisfactory as the large dose of morphine alone for the relief of labor pains and is superior when the effect on fetus, respiration of the mother, average time for labor, and necessity for catheterization is considered. I should like to comment on the lack of "bladder difficulties" when the combination of drugs was used. It is, perhaps, a moot question as to

whether the morphine or the general anesthetic is responsible for the often necessary catheterization following delivery. The consensus leans toward incrimination of morphine. In these results it appears obvious that such must be the case since when morphine alone was used, the need for catheterization was greatly increased. Data accumulated from experiments on animals do not indicate that dosage plays a part in this consideration.

As mentioned earlier, one of the great disadvantages of the administration of morphine is the resultant constipation, and, as just mentioned, the resultant "bladder difficulties" when morphine is used with a general anesthetic. Whenever morphine has to be given over long periods of time it is perhaps the constipation which becomes the most obstinate problem. It can be definitely stated that the combination of prostigmine with morphine prevents the occurrence of the constipating effects noted when morphine is given alone. In my opinion, for this reason alone such a combination, even if it has no other advantage, is an important addition to our therapeutic armamentarium.

Shortly after we had reported our work (on cats) which showed a potentiative effect of prostigmine on morphine analgesia, Hardy and Wolff (24) made an enormous contribution regarding the problem of quantitative pain threshold estimation in the human. Their method, which made use of heat-light as a stimulus to the forehead, was found to be superior to any method which had previously been described. They pointed out many interesting aspects of the effects of morphine on pain and described in some detail the side reactions which accompanied the analgesia produced by morphine. For purposes of this discussion, two important considerations relevant to their work (25) may be mentioned. (1) They showed that scopolamine did not increase morphine's elevation of the pain threshold; as a matter of fact, the effect of raising the pain threshold was actually less than when morphine sulfate was given alone. They did, however, point out that such a combination induced greater psychologic effects than those obtained with morphine alone. (2) They also demonstrated that epinephrine reduced or prevented the pain-threshold raising action of morphine. In this connection, Chapman (26) has made an interesting observation in regard to the effects of the sympathetic system and pain-sense-acuity. He was unable to demonstrate that normal pain thresholds were altered after the injection of epinephrine. However, Hardy and Wolff pointed out that, although the pain-threshold raising action of morphine was antagonized by epinephrine, the side effects of morphine were also less pronounced and were of shorter duration. They suggest, as an explanation, that this action of epinephrine was due to a change in the central pain mechanism which made it refractory to the threshold-raising action of morphine. Whether or not this fits in with the popular conception that persons who are suffering from great stress and emotion are less

sensitive to pain stimuli than when they are normal, is perhaps a moot question.

The reported work of Hardy and Wolff does corroborate our findings in the animal and also our clinical and quantitative experiments in man. In other words, these authors point out that scopolamine and epinephrine reduce the pain-threshold raising activity of morphine. On the other hand, we are of the opinion that the cholinergic drug, prostigmine, enhances the pain-threshold raising activity of morphine.

One of the chief difficulties in this problem is the fact that we know so little about pain and how it is mediated. Much more work needs to be done by the physiologist in an attempt to explain the mechanism of the production of pain. There is a decided tendency to accept the hypothesis that acetylcholine is a transmitter of central stimuli. The very fact that morphine is potentiated by prostigmine, a cholinergic drug, suggests the possibility that morphine may counteract pain by altering in some manner the neurohumeral transmission of impulses in the central nervous system. There is no question but what there are many other factors, such as emotion, psychologic outlook, and well-being, which enter into the relief of pain. We are still a long way from an objective analysis of these more or less intangible aspects.

To complete our proposed projects regarding the enhancement of morphine analgesia by prostigmine, we completed (27), a few months ago, studies on human subjects making use of a modified Hardy-Wolff-Goodell pain-threshold apparatus. We believe that the modification has rendered the method of determining the pain threshold simpler and has eliminated certain possibilities of error. As an example of this, we found that a statistical analysis of 322 normal values gave a probable error of 0.231 as expressed in percentage of the mean. In this study, doses of morphine, codeine, pantopon, and dilaudid were administered in varying amounts with and without prostigmine. A report regarding the effects of prostigmine on morphine's pain-threshold raising activities was given at the Federation of the American Societies for Experimental Biology, held in Boston, March 31–April 4, 1942 (28).

When the percentage change of pain-threshold activity is plotted against time, it can be shown that prostigmine alone has no pain-threshold raising activity. In fact, pain-threshold values were decreased when this drug was administered by itself. Further, the combination of 8 mg. of morphine plus prostigmine had a greater effect in raising the pain threshold than did 16 mg. of morphine alone. Certainly, the combination is far superior when compared with the effects of 8 mg. of morphine alone. In analyzing the data, the effects of the doses only during the first two and one-half hours are included. We found that this period covered the peak of effects. After this period of time the effects of the drugs either remained unchanged for a while or gradually diminished.

The combination of the two drugs (morphine, 8 mg., plus prostigmine, 0.5 mg.) also resulted in a more rapid rise in the pain threshold. As already stated, such has been our experience in previous clinical observations (19).

The total effectiveness of the doses of morphine used alone and in combination with prostigmine requires comment. Planimeter analysis of total effectiveness indicates that the actual total effectiveness of 8 mg. of morphine plus prostigmine administered simultaneously is slightly greater than 16 mg. of morphine sulfate when given alone. That this is true potentiation and not summation became clear when we found that by planimeter analysis, the total effectiveness of 8 mg. of morphine *alone* plus 0.5 mg. of prostigmine *alone* would have produced no analgesic effect.

We have not been able to demonstrate the high percentage increases in pain-threshold values produced by opiates, as did Hardy and Wolff (25). Chapman (29), who has been working independently on pain-threshold responses to opiates, advised me that his percentage increases also are much lower than those of the aforementioned authors.

Of particular interest to us in this study, however, was the incidence of side reactions. The most common symptoms seen with 16 mg. of morphine were pruritus, somnolence, diminished time perception and muscular weakness. The intensity of these symptoms was directly proportional to the size of the dose of morphine; i.e., with a small dose of morphine the symptoms were less pronounced, and with a large dose, more severe. Although it is true that the incidence of certain symptoms resulting from a dose of 16 mg. of morphine was less when only 8 mg. of morphine plus prostigmine was given, it is also true that a similar reduction was noted when only 8 mg. of morphine was given alone. However, the combination dose produced a much greater pain-threshold raising effect than did the 8 mg. of morphine alone. Consequently, it is felt that a reduction of unfavorable reactions resulting from the use of the combination (necessitating a smaller dose of morphine) is of significance from a clinical standpoint. In other words, it seems of practical importance to indicate that not only does the prostigmine enhance the analgesic effects of the small dose of the opiate to a point where it was nearly equivalent to the large dose of the opiate alone, but it also decreased the side reactions as observed when the large dose of the opiate was given by itself. Certainly, with a view to the more rapid rehabilitation of combat patients, any drug or combination of drugs which relieves pain and at the same time reduces side reactions, such as muscular weakness, nausea, and diminished time perception, would be preferable to a drug causing these undesirable manifestations.

While we were preparing this paper, an article by Andrews (30) recently appeared. By means of the Wolff and Hardy technic and using two normal persons and performing apparently only a few experiments, Andrews came to the conclusion that the combination of prostigmine

and morphine was not significantly more effective in raising pain threshold than was morphine alone. From his report, it is not clear whether the persons who received the combination dose were the same as those who received only the morphine alone. We have found that it is very important that each subject be his or her own control. Further, Chapman (31) and I independently have observed that some individuals appear to be congenitally refractive to as much as 8 mg. of morphine. When only a very small number of subjects is used, this factor has an important bearing on the final outcome of the results.

It is of interest in Andrews' paper to note that he obtained a highly significant potentiating action when he combined morphine with prostigmine and compared it with a similar dose of morphine alone in six-week post addicts. His comment on this enhancement is, ". . . but the mean curve was abnormally low."

We are confident that clinical experience of other workers, those of our own, and the quantitative data which we have presented, clearly indicate that prostigmine enhances the analgesic effect of morphine in the human. As I indicated earlier, just exactly how this comes about is not known.

We are engaged in further studies along these same lines and plan to make use of the electroencephalograph which we hope will give us a more objective end point for pain-threshold. Perhaps these experiments may give us some insight as to the mechanism of pain reactions —at least that is our hope.

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