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HAZARDS IN THE THERAPEUTIC USE OF MORPHINE

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SERTÜRNER, a pharmacist, isolated the active principle of opium, in 1805, naming it morphium after the Greek god of sleep and dreams, Morpheus. The therapeutic emphasis over the years has been more and more directed to its analgesic effects rather than the sleep-producing properties its name suggests.

It has been our experience that the dangers of addiction from the use of morphine are far better known to the medical profession than the hazards of its use in treatment of certain pathological conditions not uncommonly encountered in the practice of medicine.

While morphine remains, after 145 years, indispensable in the physician's armamentarium for the relief of pain and suffering, it is the purpose of this paper to present those pathological states in which morphine seems clearly contraindicated and other conditions in which morphine should be used only with great caution. The need for such a presentation seems clearly indicated in view of the oft repeated principle that a narcotic should never be used when another drug will accomplish the same purpose. Indeed, Beecher[1] has editorially stated that many abuses in the use of morphine are prevalent and difficult to justify. He stressed the relief of severe pain as the important use of morphine.

PHARMACOLOGICAL ACTIONS

The clinical object of using morphine, the relief of pain, is an entirely central effect, and thought to be in the thalamus rather than as formerly supposed in the cortex.[2] Wolff, Hardy and Goodell[3] have found that there are three components in the mechanism of relief of pain by morphine: (1) it raises the threshold for pain perception; (2) it alters the pattern of reaction to pain, enabling tolerance of the experience of pain freed of its implications; (3) it may induce sleep which, in itself, raises the threshold of pain by approximately 50 per cent. The relaxation, disappearance of fears, euphoria and other psychologic effects outlast the purely analgesic action by many hours. It has been noted

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that occasionally, especially in women, excitation of the central nervous system may occur, manifested most frequently by nausea and vomiting but rarely by delirium and convulsions.[2] Salter and White,[4] in a detailed discussion of morphine sensitivity, comment on the fact that the highly neurotic patient not uncommonly responds to morphine with restlessness, sleeplessness, and even confusion. Morphine has a relatively poor central anticonvulsant action and may, through its stimulating action on the spinal cord, increase this tendency.

The well known constricting effect on the pupils is also a central effect, the exact mechanism of which is unknown. A constant physiological, and potentially dangerous, action is the primary depression of respiration by direct action on the respiratory center, occurring even with small doses, but proportional in degree to the dosage. In human morphine poisoning, respiratory arrest is the usual cause of death.[2] Since the respiratory center may also be affected by pathological conditions, such as anoxia, produced by severe hemorrhage, and increased intracranial pressure, caution in using morphine in such states is indicated.

In small doses morphine dulls and in large doses abolishes the cough reflex, a fact of some importance clinically.[2] When repeated doses of morphine seem probable, as in the treatment of acute coronary thrombosis, one should keep in mind that the maximum depression of the respiratory center occurs within two hours when morphine is given hypodermically. Rather than delay an hour or two in attempting to control severe pain with hypodermic injections, Bieter[5] recommends intravenous injection of morphine since it has been demonstrated by Dripps and Comroe[6] that by this route the maximum respiratory depression is produced within ten minutes. These latter investigators also found that all phases of respiration—rate, minute volume, and tidal exchange—were depressed by morphine.

Another important action of morphine in therapeutic doses (8 to 15 mg.) is its spasmogenic action on the smooth muscles of the gastrointestinal, biliary, genitourinary and respiratory tracts.[7] Clinical advantage is occasionally taken of the constipating effect of morphine, although in other instances it may be quite annoying. The action of morphine on the stomach in lessening gastric motility, increasing the tone of the antrum and spasm of the pyloric sphincter may delay emptying of the stomach for twelve hours or more and contributes about one-half to the total gastrointestinal delay which is the basis of morphine constipation.[2] Propulsive movements of the small and large intestine are decreased while there is an increase in the amplitude of the nonpropulsive type of motility. This causes dyskinesia of the movements of the small and large intestine,[8] resulting in delay in passage of their contents. Additionally, both biliary and pancreatic secretions are diminished by morphine which delays digestion in the small intestine.

The effect of morphine on the biliary tract is quite interesting since it is so frequently used in biliary colic. Butsch, McGowan and Walters[9] have shown that therapeutic doses of morphine will cause a marked increase in the intrabiliary pressure, from a normal of less than 20 mm. of water to over 200 mm. of water apparently due to spasm of the sphincter of Oddi. Symptoms simulating biliary tract disease were occasionally encountered. The spasm was not relaxed by atropine. These experiments suggest the cerebral origin of the relief of biliary tract pain with morphine. On the basis of these facts, Ivy[10] has suggested that the production of biliary colic by 10 mg. of morphine in the cholecystectomized patient is probably diagnostic of spasm of the sphincter of Oddi, or the so-called postcholecystectomy syndrome.

A similar effect on the normal human ureter has also been demonstrated by Ockerblad and Carlson.[11] They found that morphine increased the tone and the amplitude of contractions, an effect appearing within several minutes and persisting for several hours. Atropine can eliminate the morphine-induced spasm. In ureteral colic it was found that morphine increased the patient's pain and distress for a few minutes at which time the cerebral effect of morphine became effective in relieving the pain. Occasionally, a stone is passed shortly after the administration of morphine due to the increased stimulation.

The production of nausea and vomiting by morphine is purely of central origin resulting from direct stimulation of the medullary emetic center. Nausea and vomiting occur fairly frequently, especially in women. In forty-one normal adults between the ages of 18 and 31, David[12] found that sixty-three per cent became nauseated and 27 per cent of this group vomited. However, many patients who are not suffering from pain react by vomiting, whereas if they really need the drug, vomiting does not occur.[4] In some conditions the frequency of the nauseant and emetic tendency may be a distinct disadvantage, since it is unpredictable as to occurrence and severity.

Morphine is readily absorbed from the stomach and the subcutaneous tissues. It is partly excreted from the body but is mainly destroyed in the tissues. The liver plays a major part in its detoxification. The substance bound with morphine in this process is thought to be glucuronic acid.[13] Excretion is almost wholly by way of the urine, though very small amounts may be excreted in feces, gastric juice, sweat and milk. The amount of bound morphine excreted in urine is three to ten times higher than that of free morphine. Only small amounts of bound, and no free, morphine were found in bile, which strengthens the belief that the site of morphine conjugation with glucuronic acid is the liver.[14]

A fact of some clinical importance that is not generally known is the similarity of morphine to the cholinergic group of drugs. Slaughter and Gross[15] pointed out the similar physiologic actions of morphine and acetylcholine and concluded that morphine met the postulates of a cholinergic drug, namely: (1) depressed serum cholinesterase in vivo; (2) was potentiated by prostigmine, a cholinergic drug; (3) and was antagonized by an anticholinergic drug, atropine.

LIVER DISEASE

It is our opinion that the use of morphine is contraindicated in the presence of liver disease. The clinical observations that patients with such disease tolerate morphine poorly and that morphine may be a contributory factor in causation of complications or death are not widely known. Many textbooks do not mention this precaution. The most common liver disease in which morphine is used, and with its most devastating effect, is cirrhosis. The usual reason for the exhibition of morphine in this disease is for the alleviation of pain or in the treatment of gastrointestinal hemorrhage due to ruptured esophageal or gastric varices. These manifestations may be treated without knowledge of the underlying diagnosis. That abdominal pain is a common manifestation of cirrhosis is indicated by the study of ninety-three autopsied cases in which approximately 50 per cent of the patients experienced this symptom.[16] Watson[17] also emphasized that typical biliary colic occurs in some noncalculous cases of cirrhosis.

Mallory,[18] in a discussion of a case of cirrhosis in a youth who lapsed into coma soon after being given 8 mg. of morphine, was impressed by the incidence of such patients who, following a single dose of morphine, develop irreversible coma. Fagin and Thompson[19] reported that in six of fifteen patients with cirrhosis of the liver dying in coma, development of stupor progressing to coma followed within a few hours after the administration of 10 to 15 mg. of morphine. Murphy, Chalmers, Eckhardt and Davidson[20] in a study of forty patients with hepatic coma also confirmed these findings and stated that as little as 10 mg. of morphine may induce coma lasting up to three days or until death ensues. Capps and Barker[21] in discussing the treatment of infectious hepatitis cautioned against the use of morphine, since they have encountered acute fatal morphinism after 30 mg.

The basis for the deleterious results of morphine in liver disease has been previously indicated. Morphine is primarily destroyed in the body by detoxification with glucuronic acid, a process taking place primarily in the liver. Furthermore, Lichtman[22] has stated that glucuronic acid production and synthesis are diminished even in minor hepatic insufficiency. Experimental confirmation of this was presented by Gross[23] who showed in animals, after liver damage induced by chloroform or carbon tetrachloride, that the excretion in the urine of free morphine is increased and that of the glucuronide or bound morphine decreased. This occurred without any corresponding increase in the total morphine excreted. Another factor of some importance in this respect is that the rate of glucuronic synthesis is based on the concentration of glycogen in the liver.[24] Glycogen stores are diminished in liver disease as well as by anoxemia, debility and starvation which would add to the diminution in detoxification of morphine. This indicates that in liver damage the body is less able to get rid of morphine, thus permitting more intensified and prolonged action than in the patient without liver damage.

Illustrative Cases. We have encountered several instances of this deleterious effect of morphine in the presence of liver disease and present two illustrative examples.

Case I. A 49 year old white woman was admitted in August 1949 in coma. She was a known alcoholic of many years' duration. In July 1948 she had been hospitalized at another hospital and a diagnosis of portal cirrhosis complicated by ascites and jaundice had been made. She improved on treatment and in May, 1949 a pelvic operation, which the patient withstood well, had been performed. She had been in her usual health until four days prior to admission when she went on a drinking spree. One day prior to admission she complained of nausea and vomiting. Hallucinations and movements interpreted by her husband as convulsions were noted and a doctor was called. Two hours before her admission 15 mg. of morphine sulfate was administered hypodermically. On admission the patient was comatose with long periods of apnea being noted. Respiratory rate of 4 to 6 per minute was noted. Her pupils were markedly constricted and many bruises were present on her body. The liver was hard and its edge was palpable 5 cm. below the right costal margin in the midclavicular line. There was generalized lack of reflex response. She was immediately placed in an oxygen tent and intravenous glucose started. Analeptics were also given. Reflexes began to respond after two hours. Stupor continued for three hours when consciousness returned. She remained disoriented for three days.

Laboratory studies on admission revealed normal spinal fluid dynamics and findings, a blood sugar of 309 mg. per 100 cc., carbon dioxide combining power of 31 volumes per 100 cc. and nonprotein nitrogen of 38 mg. per 100 cc. The hemogram and urinalysis were not remarkable. A fasting blood sugar two days after admission was normal. Liver function tests showed moderate impairment and a needle biopsy revealed cirrhosis with fatty metamorphosis.

Comment. In this case of cirrhosis, respiratory depression and coma occurred shortly after the administration of morphine. The alleged convulsions may have represented "rum fits" as hypoglycemia was ruled out by the elevated blood sugar on admission. In alcoholism, and especially delirium tremens, morphine is also poorly tolerated and this factor may have exaggerated the response in this patient with known liver disease. The use of morphine in this patient with cirrhosis seems clearly in error.

Case II. A 35 year old white man was admitted in November 1949 because of hematemesis. He had been a confirmed alcoholic for the past ten years. A diagnosis of portal cirrhosis was made in 1947, following a laparotomy for a right upper quadrant mass.

He had been drinking heavily for three weeks prior to admission. Swelling of the abdomen and legs were noted two days prior to admission. Three hours before his admission he vomited an estimated 1½ pints of bright red blood. No previous hematemesis had been experienced. On admission the patient appeared well developed, slightly tremulous, well oriented and alert, not apprehensive, cooperative, able to walk, and breathing fairly easy.

Physical examination revealed blood pressure to be 150/90, pulse 140. A moderate degree of scleral icterus and spider hemangiomas over the upper anterior thorax were noted. The heart and lungs were not remarkable. A hard liver, the edge 7 cm. below the right costal margin in the midclavicular line, was palpated. A fluid wave was elicited. Mild edema of the lower extremities was present.

On admission, the patient was placed at absolute bed rest and given 15 mg. of morphine sulfate. He was given 1500 cc. of properly typed whole blood. Four hours after admission another injection of 15 mg. of morphine sulfate was administered. Because of evidence of shock shortly after this, he was placed in an oxygen tent with the foot of the bed elevated. When he was seen eight hours after admission, the blood pressure was 80/40, respirations between 6 and 10 per minute and the patient's pupils were extremely small and unreactive to light. He was in coma from which he could not be aroused. Coramine and caffeine preparations were administered but the respiratory rate became progressively slower and he died ten hours after admission. Autopsy findings revealed severe portal cirrhosis with ruptured esophageal varices.

Comment. It seems clear that the respiratory failure in this case was caused by the morphine. On admission, despite the hematemesis, the patient was ambulatory and blood pressure was maintained. After onset of treatment there was no further hematemesis or gross evidence of bleeding. The findings terminally were too obviously similar to acute morphinism to overlook. There is usually a large margin of safety between therapeutic dosage (8 to 15 mg.) and toxic dosage in the patient who does not have one of the conditions, such as liver disease, in which there is accentuated sensitivity.

In addition to advanced liver disease, the factor of severe hemorrhage adds an additional burden to a damaged liver. The reason for the use of morphine in this case probably was the restlessness and apprehension associated with the loss of blood and best treated by blood replacement. In this case, then, there seemed to be actually little indication for the exhibition of morphine. In an already damaged liver, the additional anoxia induced by loss of blood still further impairs the function of the liver and makes it more difficult than previously to detoxify morphine by conjugation. These deleterious results, we believe, will be prevented by assiduously avoiding the use of morphine in all cases of known or suspected liver disease and its complications, especially hemorrhage.

ASTHMA

Morphine has been used in the treatment of bronchial asthma with apparent good results in some cases. However, analysis of reports and of the physiological actions of morphine leads one to the definite conclusion that morphine is contraindicated in the presence of asthma.

Balyeat[25] reported five deaths following closely the administration of morphine to chronic asthmatics. Vaughan and Graham[26] stated that death from asthma was uncommon and reported only eight deaths in acute intractable asthma "among the several thousand asthmatic patients" examined by them. Of these eight, four had received morphine shortly before death. Unger and associates[27] confirmed this in reporting twenty-one cases in which asthma was the sole or main cause of death. Six of these patients were known to have received morphine prior to death, a not infrequent happening in their experience.

The deleterious effect of morphine in asthma has usually been explained on its depression of the respiratory center, its decrease of the cough reflex making it more difficult to get rid of the bronchial secretions, and its spastic effect on the bronchial musculature. Prickman and Morgan[28] have observed that no matter how effective morphine may be in quieting the patient and relieving his apprehension, the asthma itself is not benefited and the wheezing continues unabated. Indeed, in one case in which morphine had been given respirations were reduced to five a minute but the asthmatic wheezing continued. In this respect, the investigations of Curry and his associates[29] are quite pertinent. They have demonstrated that severe attacks of asthma are accompanied by increased pulmonary responsiveness to cholinergic drugs. Rackemann[30] and Curry[29] have suggested that the deleterious effects of morphine in asthma are in part due to its cholinergic action on the bronchial tree. For these reasons, there seems little reason for the use of morphine in asthma.

HYPOTHYROIDISM

Lund and Benedict[31] noted during an operation on a female patient, who was not myxedematous but had a basal metabolic rate of minus 18, slow shallow respiration which suggested overdosage with morphine. She had been given 10 mg. prior to surgery. It was later discovered that the patient had two previous similar experiences with morphine. This led them to a study of the effect of morphine on various groups of rabbits. In the normal group, morphine caused a 10 per cent drop in the metabolic rate. There was no drop in hyperthyroid rabbits given morphine but a 20 per cent drop in hypothyroid rabbits. In humans, excessive doses of morphine are well tolerated in hyperthyroidism but hypothyroid patients are peculiarly sensitive to morphine and therapeutic doses may prove fatal. Benedict[32] encountered a myxedematous patient with a basal metabolic rate of minus 20 who was given 16 mg. of morphine preoperatively. Respirations dropped from 20 to 7 per minute and the patient could hardly be aroused for some time. She was given thyroxin and twenty-one days later, when her basal metabolic rate was on the plus side, dosages of 8 and 11 mg. of morphine were well tolerated. In reviewing 102 cases of myxedema and 128 cases of hypometabolism, Benedict found that in one case of myxedema with a basal metabolic rate of minus 20, death followed shortly after the administration of 8 mg. of morphine. In a case in which the basal metabolic rate was minus 19, but myxedema was not present, respirations went from 20 to 10 per minute after 10 mg. of morphine preoperatively and two similar doses postoperatively. Sensitivity in Addison's disease in which the basal metabolism is lowered has also been reported; the use of morphine is strictly contraindicated in this disease.[4]

The exact mechanism of the sensitivity of the hypothyroid patient to morphine is not known. Perhaps the decreased rate of oxidation in the tissues sensitizes, even more exquisitely than usual, the respiratory center. At any rate, morphine is clearly contraindicated in hypothyroidism and perhaps in other states in which the basal metabolic rate is decreased.

KYPHOSCOLIOSIS AND CHRONIC COR PULMONALE

Not well appreciated is the fact that the most frequent cause of death in "hump backs" is congestive heart failure with an average age at death of 30. Even without cardiac failure, the patient with kyphoscoliosis who has any sort of respiratory embarrassment is peculiarly sensitive to morphine. Schroeder[33] reported the effects of 10 mg. of morphine given to an eclamptic patient with kyphoscoliosis. She nearly became asphyxiated, with a respiratory rate of 2 to 3 per minute. Daley[34] presented three fatal cases occurring in patients with kyphoscoliosis and congestive heart failure, death occurring in each case within an hour and a half after administration of 6 to 16 mg. of morphine. In the third case presented by Daley, the sensitivity to morphine was appreciated and therefore only 5 mg. was given. Despite this small dosage, respiratory depression and death followed. Possibly another factor in this group is that such patients are below average weight and would, for this reason, not tolerate the usual adult dosage.

Katz and Chandler[35] reviewed this subject in presenting a fatal case and a severe reaction to morphine in patients with kyphoscoliosis and heart failure. In the patient who survived 10 mg. after an episode of coma with respiratory depression, a test dose of 4 mg. of morphine caused the respirations to drop from 26 to 16 per minute and to become

Cheyne-Stokes in character. Cheyne-Stokes respiration may occasionally be detected in normal sleeping people and does not indicate severe respiratory damage unless it is fully developed and prolonged, according to Dripps and Comroe.[6] The same authors found Cheyne-Stokes respiration to occur in three of nine patients given intramuscular and in two of six patients given intravenous morphine.

The vital capacity of patients with kyphoscoliosis without heart failure is low, averaging from 800 to 1850 cc. in six cases.[34] Any respiratory or cardiac difficulty will tend to decrease this submarginal vital capacity and serve to cause decreased oxygen saturation of the blood. Katz and Chandler[35] feel that the asphyxia from morphine in this group of patients is caused by its central respiratory depressant action, diminution of cough reflex, the cholinergic action accentuating bronchial spasm and the pain-relieving action resulting in diminished muscular tone.

They also believed that any chronic lung condition in which cardiac decompensation has developed will afford a similar fertile background for development of severe morphine poisoning with small or therapeutic doses of morphine. Chronic cor pulmonale is such a condition in which severe respiratory depression has followed therapeutic dosage of morphine. This is substantiated by Spain and Handler[36] who reviewed sixty autopsied cases of chronic cor pulmonale. While morphine appears to make such patients comfortable, few recover because of the increased anoxemia due to the suppression of the cough reflex causing purulent bronchial secretions to puddle in the pulmonary tree. The basic underlying factor in forty of these cases was diffuse obstructive emphysema, either primary or secondary. In these conditions, as in kyphoscoliosis, vital capacity is sharply reduced, and the same factors relating to the action of morphine apply.

HEAD INJURIES

The use of morphine in injuries and accident casualties is widespread and its effectiveness in relieving pain in those situations is unquestioned. However, in the case of head injury morphine should be withheld. Munro[37] strongly emphasized the danger of using morphine in cases of cerebral trauma. He pointed out that concussion alone may alter and even paralyze the respiratory center in the medulla. Increased intracranial pressure similarly affects the respiratory center. To add the further burden of another factor, morphine, which depresses the respiratory center, seemed folly or worse. He gave as a good general rule, "No morphine where increased intracranial pressure is suspected." Furthermore, morphine may obscure signs and symptoms which may be of great importance in diagnosis and therapy. The effect on the sensorium and miosis of the pupils may well confuse the neurologic examination in these cases.

Experimentally, Phillips[38] demonstrated that morphine in doses having little effect on the normal cat will produce signs of respiratory failure if it is preceded by even slight degrees of cerebral trauma. The tolerance to morphine is definitely lowered by a blow or injury to the head.

Another factor mitigating against the use of morphine in cases of cerebral trauma is the effect of the drug on the spinal fluid pressure. Gurdjian, Webster and Sprink[39] studied the effect of morphine on the spinal fluid pressure in normal patients and in a group of cases with head injury. It was determined that while there is a tendency for small insignificant rises in the normal group, there were conspicuous increases in the spinal fluid pressure in the head injury group. The more severe the injury the more marked was the increase of the spinal fluid pressure. The mechanism for this increase was obscure. It was thought that since this group has cerebral edema, hemorrhage, or derangement of the circulation, morphine might increase the state of partial anoxia already present. It was their conclusion that morphine was contraindicated in cases of head injury because, in addition to depressing respiration and masking symptoms, the increase in spinal fluid pressure could well endanger life. Presumably the same logic would apply to various conditions in which there is increased intracranial pressure such as brain tumor and cerebral edema.

GASTROINTESTINAL HEMORRHAGE

The use of morphine in severe gastrointestinal hemorrhage has been customary in the past but the current trend is either against its use entirely or its use with caution. The cause of this variety of bleeding in 60 to 80 per cent of the cases is peptic ulcer, with the duodenal variety predominating. However, in two large series reported by Schiff[40] and Thompson and McGuffin,[41] liver disease with esophageal varices was responsible for 10.5 per cent and 9.2 per cent, respectively, of cases of gastrointestinal bleeding. In these cases with underlying liver disease, morphine, as previously noted, is contraindicated. Hemorrhage in a case of cirrhosis may by itself precipitate cholemia and coma to which grave course of events the addition of morphine actions should be avoided. In a sizeable proportion of cases of gastrointestinal hemorrhage the etiologic diagnosis is not quickly apparent, nor may it be after diagnostic study, but it behooves the physician to attempt to determine the presence of liver disease before prescribing morphine. In this regard, we have found the use of the 5 mg. bromsulphalein test, the subject of a recent discussion by Zamcheck and associates,[42] to be quite helpful in determining the presence of liver disease in cases of gastrointestinal hemorrhage.

What, then, are the possible indications for morphine in the majority of cases of gastrointestinal bleeding? It has been repeatedly observed that patients with peptic ulcer have alleviation of their usual pain when bleeding begins. In the presence of bleeding and pain, an additional complication such as penetration or perforation of the ulcer should be considered. Actually, pain is not a serious problem in most cases of gastrointestinal hemorrhage. The usual reasons for which morphine is administered in these cases are restlessness, excitement and apprehension. These symptoms are increased when shock is present. These symptoms are due to loss of blood and replacement of blood, not morphine, will alleviate them. The advisability of the routine use of morphine in shock is questioned and will be taken up separately. In the condition of gastrointestinal hemorrhage, a sedative may well be needed but we do not feel that morphine should be used as a sedative here or in other instances. Chloral hydrate, barbiturates and paraldehyde will better serve the purpose when sedation is required.

Welch[43] flatly stated that use of morphine is contraindicated in massive gastrointestinal hemorrhage. On the other hand, Baker[44] in a study of 540 patients with bleeding peptic ulcer used morphine routinely for sedation and reported no ill effects from its use. We agree with Jones[45] that morphine should not be used because of its tendency to cause nausea and vomiting which is especially undesirable in cases of gastrointestinal hemorrhage and cannot be predicted in a given case. The abnormal duodenal spasm which morphine induces is also not desirable.

Another factor that we believe should be considered is the effect of severe hemorrhage on the liver, even in normal patients. Gillman and Gillman[46] in a study of patients dying accidentally found that, histologically, the liver is more rapidly and severely affected by hemorrhage than by other stimuli. The liver would appear to be especially sensitive to the effects of anoxia. Experimentally, Fine, Seligman and Frank[47] have indicated that in hemorrhagic shock, damage to the liver is of central importance in determining survival of the animal. It appears to us that these investigations indicating liver impairment in hemorrhage afford additional reason for the withholding of morphine in gastrointestinal hemorrhage, in view of the deleterious effects of morphine when liver function is impaired.

SHOCK

Standard treatment of shock, hemorrhagic or traumatic, has included the use of morphine. As a result of observations during World War II there have occurred changes in the point of view as to routine use of morphine in shock. The indications for morphine here have been pain, excitement, apprehension and restlessness. Beecher[48] observed 215 soldiers with extensive wounds and found that only 25 per cent had severe pain or wished pain relief. The incorrect belief that extensive wounds are associated inevitably with pain has led to the needless and perhaps hazardous use of morphine.

Elman[49] has observed that in some human burns severe pain may also be absent. Experimentally, this latter author has presented data to the effect that morphine administered to dogs with severe experimental burns increased the mortality. There is thus the possibility that morphine in human burns without pain may act similarly. Powers, Reed and Gregersen[50] noted the usual respiratory depression in normal dogs given 1/100 of the lethal dose of morphine intravenously. In dogs with experimental hemorrhagic shock there was little difference in reaction to the morphine than in the normals, but in the dogs with traumatic shock there was a further drop in blood pressure, oxygen consumption, and cardiac output.

In a recent important editorial[51] the use of morphine in shock was reviewed. In shock, either traumatic or hemorrhagic, there is arterial vasoconstriction, low circulating blood volume, poor cardiac output, slow capillary blood flow, reduced peripheral circulation and depression of blood pressure. Morphine, the editorial continues, even in moderate doses, in shock, further depresses blood pressure, lowering the blood volume and further diminishing cardiac output; it also antagonizes vasoconstriction, dilating cutaneous vessels to further slow the blood and increase capillary stagnation. Morphine depresses the medullary center and stimulates the reflexes and spinal functions. It produces nausea, vomiting and sweating which increases fluid loss. The editorial stated that morphine is contraindicated in shock. We might add that shock also decreases the basal metabolic rate which state apparently has a greater sensitivity to the usual dosages of morphine. There has also been mentioned the effect of shock in impairing liver function rather quickly and severely. This factor cannot be overlooked in morphine therapy since it plays such a vital role in detoxification of the drug.

If pain is absent, the other symptoms of restlessness, excitement and apprehension, for which morphine was given, are caused by cerebral hypoxia which will be alleviated by blood replacement and not morphine. As indicated previously, sedative drugs are more logical to use for these symptoms than morphine.

Another aspect of the use of morphine in shock was also emphasized by Beecher.[1] Failure to realize that subcutaneous morphine will be only poorly absorbed, if at all, when the peripheral circulation is sluggish as a result of cold or low systemic blood pressure as in shock, leads to difficulty. Because of failure to get pain relief from the injected drug, second and third doses of morphine are often given. Later use of measures to improve the circulation results in all or a great part of the unabsorbed drug rapidly entering the circulation with resultant acute morphine poisoning. This condition should always be looked for in persons admitted to the hospital in shock who have had emergency treatment previously. In any event the safe maximum analgesic dose of morphine can be produced by 10 to 15 mg. and possibly best by the intravenous route when peripheral circulatory failure is evident.

It would appear that caution should be used in administering morphine in shock and only then if severe pain is present.

PREOPERATIVE AND POSTOPERATIVE USE

Preanesthetic medication is a standard procedure and frequently includes morphine combined with atropine or scopolamine. It is very commonly used postoperatively, frequently at regular intervals, for two to three days. As has been stated, minor yet disturbing effects such as nausia and vomiting, dizziness, lightheadedness, visual disturbances and mental confusion are common. Bieter[5] stated that these side effects occur in from 20 to 60 per cent of instances in various reports. Only four of forty normal individuals experienced no side effects as a result of 8 to 10 mg. of morphine. In the postoperative state, depression of the cough reflex may interfere with adequate respiratory drainage and contribute to occurrence of pneumonia and atelectasis. The increase of the tonus with decrease of motility of the small and large intestine induced by morphine may be contributory to postoperative distention. However, the opposite point of view is held by some.

The most thorough study of this aspect of morphine therapy is that of Strickler and Rice.[52] They compared 367 patients who underwent abdominal surgery and received morphine preanesthetically and postoperatively with 142 similar patients in which morphine was omitted. Statistically significant evidence was forthcoming that the patients who had morphine were more apt to have gas pains, vomit on the day of surgery, require catheterization on the day of surgery, and to cough after the second day. The spasmogenic action of morphine seemed to stand out. More patients in the morphine group complained of chest pain, developed pneumonia and atelectasis, wound infections, wound disruption and ileus requiring suction. Similar studies of this nature are required before a definite answer to the value of preoperative and postoperative morphine can be given. Caution is most certainly warranted.

ALCOHOLISM

Morphine is occasionally used to control the restlessness or delirium of delirium tremens or to quiet individuals agitated and excited because the effects of acute alcoholism. There is considerable evidence that this practice is fraught with danger and may result in death even in young adults otherwise normal except for the effects of acute alcoholism.

Leary[53] stated that since both alcohol and morphine are central depressants and since edema of the brain is an outstanding finding in fatal cases of alcoholism and morphinism, the use of morphine tended to accelerate these abnormal processes in the presence of alcoholism. Koppanyi[54] has found that in animals ethyl alcohol and morphine in dosage per kilogram equivalent to average human use are definitely synergistic as far as their effect on respiration is concerned. Either given alone to animals produced a decrease of about 10 per cent in minute respiratory volume; when given together a 50 to 75 per cent decrease was noted.

It has been a standing rule on the medical service of the senior author never to use morphine in persons with acute alcoholism or delirium tremens. Paraldehyde is preferred as the drug of choice for sedation of the noisy or agitated alcoholic patient.

MISCELLANEOUS

Old people, patients with cerebral arteriosclerosis and patients who have suffered cachexia and emaciation from prolonged disease are particularly susceptible to large doses of morphine.[4] Infants and young children also have a marked sensitivity to morphine. Renshaw[55] reported a fatal reaction in an 11 day old baby who had received an estimated dose of 0.15 to 0.30 mg. and at autopsy revealed no cause of death. Another interesting finding in infants is the occurrence of congenital morphine addiction in children born of addicts. Pehu[56] and Pearlstein[57] both reported addicts having newborn infants who manifested abstinence symptoms which began about three days after birth. This would indicate that morphine passes through the placenta in sufficient quantity to cause fetal addiction.

The use of morphine is not indicated in convulsive disorders since in addition to the increase in cerebrospinal fluid pressure, it also increases the reflex excitability of the spinal cord. Occasionally morphine is used in intractable cases of pruritus, usually without much success. Actually, exacerbations of itching are more apt to occur since morphine has pruritic properties. David[12] found that 40 per cent of forty-one normal adults to whom morphine was given had itching as a side effect.

Acute urinary retention as a result of the tonic action of morphine on the detrusor muscle is most apt to occur in the postoperative state and in the patient with an hypertrophied prostate or ureteral stricture. Morphine also exhibits a lowering of urine flow, reduction in renal plasma flow and an increased reabsorption fraction, all of which results in decreased urine output in the normal human patient.[58] This antidiuretic effect of morphine was noted by Ferrer and Sokoloff[59] in three of nine patients with congestive heart failure. Mercurial diuresis is also apparently inhibited by morphine. The exact mechanism of the antidiuretic effect is not known.

SUMMARY

The conditions which have been discussed and in which morphine should be used cautiously if at all are listed in Table 1. The rational use of morphine in the relief of severe pain has been emphasized without detriment to the analgesic properties of this most valuable drug.

TABLE 1

MORPHINE CONTRAINDICATED IN:

1. Liver disease, acute and chronic.
2. Bronchial asthma.
3. Primary hypothyroidism.
4. Pituitary myxedema.
5. Adrenal insufficiency.
6. Kyphoscoliosis.
7. Chronic cor pulmonale.
8. Chronic pulmonary emphysema.
9. Head injuries.
10. Alcoholism and delirium tremens.
11. Convulsive disorders.

USED WITH CAUTION IN:

1. Gastrointestinal hemorrhage.
2. Shock.
3. Postoperative treatment.
4. Infants and the aged.
5. Debilitated states.
6. Cerebral arteriosclerosis.
7. Pruritus.
8. Late pregnancy; especially prolonged use.

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