THE UTILITY OF APOMORPHINE IN CLINICAL ANESTHESIA *

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The clinical application of apomorphine as a sedative was reported by Douglas in 1899 (1). He employed it for the treatment of alcoholism. Douglas laid claim to originality in this use of the drug and described it as "one of the most prompt and sure and harmless hypnotics known to medicine" which acted "with clockwork precision." In this and subsequent reports, the same author found apomorphine to be effective in several other circumstances in which central nervous system irritability was encountered in treating neuropsychiatric patients (2, 3). In 1902 Coleman and Polk, working in Bellevue Hospital, completed a more extensive study on the utility of apomorphine as a sedative for alcoholic addicts (4). Their observations and conclusions agreed essentially with those of Douglas. Other brief but enthusiastic clinical notes appeared at the same time (5, 6).

Excitement states encountered in the practice of anesthesiology and surgery bear a definite relation to those described in earlier reports on apomorphine. Yet, from 1908 to 1933, no published account has been found that mentions such related uses for it. In 1933, one of us (E. A. R.) recommended apomorphine as an antidote to the stimulant effects of scopolamine (7). The present report emphasizes more extensive use of the depressant properties of this drug for several types of cortical stimulation seen by the anesthetist.

Occasions demanding sedation or hypnosis during circumstances in which therapeutic amounts of commonly used depressant drugs are ineffectual occur regularly. The emergence delirium described by Guedel which follows general anesthesia is not rare (8). The acute alcoholic psychoses or patients with developed or impending delirium tremens are encountered often. Drug addicts, especially those with local or systemic infection, may be extremely agitated before and after operation. Occasionally, excitability may follow the use of belladonna alkaloids, atropine and scopolamine, both of which are used extensively in hospital practice. These situations, although relatively infrequent, are important because they may be difficult to treat properly.

Apomorphine, in subemetic doses, is a valuable therapeutic aid for such patients. Its hypnotic action is prompt, dependable and safe in circumstances in which such drugs as the barbituric acid derivatives

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other opiates and paraldehyde are not sufficient. Adequate sedation with these ordinarily used depressant drugs often entails overdosage and the consequent prolonged and profound respiratory, circulatory and cerebral depression. Sedative effects following apomorphine administration become apparent in a few minutes. Patients are more easily controlled and delirium, agitation and muscular movement may cease completely or diminish to a marked degree. These effects usually are evident for several hours and are not succeeded by profound depression. Blood pressure, pulse and respiratory rates are constant with whatever changes may result from the elimination of the state of excitement. At the end of this effective interval, patients respond to ordinary doses of the usual sedative drugs.

CHEMISTRY AND PHARMACOLOGY

Apomorphine hydrochloride is a white or grayish white, crystalline isoquinoline derivative obtained by treating morphine with strong mineral acid. The crystals oxidize and acquire a greenish tint upon exposure to light and air. Apomorphine is relatively unstable and the United States Pharmacopoea recommends that it be discarded if it imparts an emerald green color when shaken with 100 parts of distilled water (9). The same authority recommends that it be stored in small, tightly stoppered, light resistant vials in quantities no greater than 0.35 Gm. Because it is unstable, some of the described accidents following its administration may be due to the presence of impurities. Early preparations of apomorphine were in an amorphous form. This preparation is extremely unstable and was responsible for delay in accurate, pharmacologic studies of the drug. Apomorphine is marketed now in tablet form (emetic doses) as the hydrochloride and is subject to federal regulation as a narcotic.

The recent tendency has been to relegate apomorphine to the group of antiquated drugs. Pharmacology texts (11, 12, 13) consider the drug not as a depressant but as an emetic. Goodman and Gilman stated, "The use of apomorphine is practically restricted to the production of vomiting." Most texts have some reference to the sedative or hypnotic action of subemetic amounts but there is very little detailed information concerning the actions of small doses. Its reputation as a dangerous and obsolete drug is based on the untoward accidents resulting from emetic doses. Present clinical experience indicates that subemetic amounts of apomorphine are free from the described hazards of respiratory and circulatory collapse and that the hypnotic action is far from uncertain. The drug itself is readily absorbed from all mucosal surfaces but its action is more certain when administered parenterally.

CLINICAL STUDIES

During the past ten years at Bellevue Hospital the staff of the Department of Anesthesia has had numerous opportunities to observe the

efficacy of small doses of apomorphine as a depressant of the central nervous system. Indications for its use were, of course, limited and infrequent. Many of the more than 300 administrations were for therapy of emergence delirium. It was used, also, as premedication for emergency operations complicated by the severe excitement of acute alcoholism, delirium tremens and severe agitation accompanying morphine addiction. The marked muscular and psychic overactivity occasionally seen before operation after hypodermic injection of scopolamine or atropine was similarly treated before the induction of anesthesia. The types of cases in which it proved useful and the typical effects are illustrated in the following brief case studies.

CASE REPORTS

Case 1. A white male, age 43, was to have first stage thoracoplasty for apical tuberculosis. He received morphine, 0.01 Gm., and scopolamine, 0.0004 Gm., one hour before operation. Anesthesia was induced with cyclopropane and maintained for two hours and twenty-six minutes. During the operation, he was given one transfusion of 500 cc. of whole blood. The induction and course of anesthesia and operation were uncomplicated. Recovery from anesthesia was accompanied by an emergence delirium which, though not severe, did not abate during fifteen minutes of observation. Because of the nature of the operation and the danger of excitement to this patient, the delirium was considered a serious complication. Apomorphine, 2.0 mg. dissolved in 10 cc. of normal saline solution, was given over a five minute period. At the completion of the injection, the excitement was noticeably diminished and had ceased completely during the next ten minutes.

Case 2. A white female, age 42, with a history of chronic alcoholism was prepared for circumferential wiring of a fractured mandible sustained during her drinking activities. She received morphine, 0.010 Gm., and scopolamine, 0.0004 Gm., ninety minutes before the induction of cyclopropane anesthesia which was accompanied by moderate excitement. The effect of premedication was considered satisfactory. Anesthesia was maintained with the to-and-fro absorption technic and an endotracheal airway for forty-five minutes. The course of operation and anesthesia was uneventful. Recovery from anesthesia was complicated by an emergence delirium which became progressively more severe in spite of oxygen administration. It required several persons to restrain the patient who was in danger of disrupting the newly immobilized fracture.

At this time, fifteen minutes after operation, she was given intravenously 1.5 mg. of apomorphine dissolved in 10 cc. of normal saline solution. The injection was completed in five minutes. The struggling diminished while the drug was being given and five minutes later the patient was removed to the ward, sleeping quietly, outwardly resembling any uncomplicated postoperative patient.

Two hours later, the patient became mildly agitated again and morphine, 0.010 Gm., was given subcutaneously. Thirty minutes later the excitement was somewhat increased and because of the concern over the fracture, a second dose of 1.5 mg. of apomorphine was administered intramuscularly. Within fifteen minutes, the patient became quiet and soon fell asleep. The excitement did not recur and further convalescence was uneventful.

Case 3. A white male, age 45, acutely alcoholic, was scheduled for debridement and reduction of a compound fracture of the leg. While drunk, he was struck by a car. He was literally "wild" on reaching the operating room. He had received morphine, 0.008 Gm., and scopolamine, 0.0003 Gm., intravenously thirty minutes before. On the carriage, the patient was restrained from chin to toes and it was feared that in removing these restraints to place him on the operating table he might cause further serious damage to the injured leg. He was given 1.5 mg. of apomorphine intramuscularly. Twenty-five minutes later the patient was quiet. He was given spinal anesthesia and the operation was completed during the next hour without further complication.

Case 4. A white male, age 38, in an acute alcoholic episode, was scheduled for an emergency laparotomy for perforated peptic ulcer. Before he was brought to the operating room typical delirium tremens developed. Operation was postponed and 15 cc. of paraldehyde was given by rectum. His muscular twitching and apprehension continued in spite of an additional 10 cc. of paraldehyde. The surgeon decided that operation should be delayed no longer and the patient was given morphine, 0.01 Gm., and scopolamine, 0.0004 Gm., and brought to the operating room one hour later. He was no better.

The patient was observed for forty-five minutes longer without change in his condition. He was then given 2.0 mg. of apomorphine intravenously. After twenty minutes, the muscular movements had ceased almost completely, the patient seemed fairly well oriented and not significantly apprehensive although alert. Anesthesia was induced with pentothal, maintained with ether and continued for eighty-two minutes without complication.

Case 5. A white male, age 56, a morphine addict, was scheduled for repair of wound dehiscence. Nine days previously, a stab wound of the abdomen had been repaired. The patient was given morphine, 0.015 Gm., and scopolamine, 0.0004 Gm., but after ninety minutes, the preexisting agitation and incoordination were unchanged. He was given 2.0 mg. of apomorphine intravenously and within ten minutes, restlessness, fear and muscular activity ceased. Five minutes later, cyclopropane anesthesia was instituted rapidly with moderate excitement and was continued for eighty-eight minutes. The course of anesthesia was uneventful though the contemplated operative procedure was expanded to include an intestinal anastomosis.

Case 6. A white male, age 23, with acute appendicitis had been given 0.01 Gm. of morphine in the emergency ward one hour before coming to the operating room. His pulse rate was 94 and temperature 101.2 F. At this time, 0.0004 Gm. of scopolamine was administered intravenously. Within a few minutes he became talkative, noisy, restless and unreasonable, moving about on the carriage so that he needed to be restrained. His skin was slightly flushed but his pulse, blood pressure and temperature were not significantly altered. It was decided that he had received two doses of scopolamine, one of which was not recorded, or that he was showing an idiosyncrasy to a single dose of the drug. Apomorphine, 1.5 mg., was administered intramuscularly. During the next twenty-five minutes, the signs of cerebral stimulation gradually subsided and the patient's condition seemed satisfactory for anesthesia. Nitrous oxide-oxygen-ether sequence was employed uneventfully to complete the operation.

These case reports represent typical examples of the satisfactory safe use of apomorphine. It will be noted that it is not suggested as

a substitute for other depressant drugs except in these special circumstances. The experience here with the drug is limited to surgical patients. Satisfactory results are conditioned by the care exercised in its use and the selection of patients. No accidents or untoward effects have been observed here. Its use, however, is carefully limited since the underlying causes of the excitement states dealt with are not entirely explained.

ADMINISTRATION AND RESULTS

The sedative dose of apomorphine varies from 1 to 2 mg. for the average adult patient. Since the commercial tablet contains several times this amount, most of it must be discarded after it is dissolved. The remainder is diluted to a volume of 10 cc. with sterile normal saline solution. This diluent is used in preference to distilled water to avoid possible laking of red blood cells. When the solution is administered intravenously, the rate of injection should be slow, occupying four or five minutes. The predisposition to nausea and emesis in surgical patients accentuates the need for these essential precautions of dilution and slow injection in order to eliminate any emetic effects from the drug. Apomorphine is effective also when given intramuscularly in similar doses. It is rapidly absorbed from the site of injection and need not be diluted or given slowly.

If the results of the initial dose are considered inadequate after twenty minutes, it is safe to repeat the injection using half the amount. Should the excitement recur after several hours, the initial dose may be repeated.

Desired sedative effects following intravenous administration of apomorphine are noted within ten minutes and usually last less than two hours. When the drug is given intramuscularly, the effects become evident in about twenty minutes and last two hours or more.

CONTRAINDICATIONS

The indication for apomorphine is provided by the patient who is excited or delirious because of cerebral stimulation. A comparable clinical picture may and frequently does result from cerebral hypoxia. Apomorphine should be avoided whenever asphyxia or oxygen want from any cause may be a factor in the excitement or delirium. The differentiation should be obvious if one can recognize hypoxia from respiratory obstruction, shock, pneumothorax, atelectasis or any of the conditions interfering with an adequate cerebral supply of oxygen.

SUMMARY

Subemetic doses of apomorphine hydrochloride have been used to treat various excitement states seen in relation to anesthesia. Several typical cases are discussed. The properties of apomorphine and its

manner of administration as a sedative are briefly reviewed. When used properly, this drug seems to be a safe and reliable therapeutic aid.

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