Clinical Analgetics

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CLINICAL ANALGETICS

CHAPTER 1

GENERAL CONSIDERATIONS

THE PURPOSE of this monograph is to provide a concise, practical guide on analgetics for the general practitioner, dentist, pharmacist and medical student. For this reason, the text is limited to a description of the more commonly employed agents with special emphasis on pharmacologic effects in man, dosage forms, toxicity, indications and contraindications. General references and review articles are listed at the close of each chapter.

General anesthetics are not described in the text although local anesthetics are included because of their wide use in pain situations. Analgetic agents are defined as those materials which when administered provide relief from pain by means other than reduction or removal of the causative factor. For example, surgical section of the fifth nerve in the treatment of *tic doloreux* does not come under the scope of this text. An alcohol block is however considered as an analgetic by this definition. Another example is the use of morphine in the treatment of biliary colic. Ten mg of morphine sulfate increases intrabiliary pressure, yet it provides pain relief by virtue of the central action of morphine. Amyl nitrite, under similar conditions, alleviates pain by reduction of intrabiliary pressure (the cause of pain) and is not considered an analgetic. Therefore, the host of materials used in the treatment of disease and which indirectly alleviate pain, are not considered in this text as analgetic agents. Therapeutic agents to remove or reduce the cause of pain are, of course, more desirable than analgetics. However, the list of agents used in all pain situations is so formidable as to warrant their exclusion from this description of analgetics. Beck-

man, for example, names at least eighty-four agents used in the treatment of pain.

The salicylates and similar compounds occupy a unique position since it is questionable whether they are analgetics, as they may exert their effect by removing or altering the cause of pain. However, in view of the common use of these agents for analgetic effect, they are included in this text with the reservation that they may not be true analgetics.

The nomenclature of the constituents of opium and its derivatives is well established. With the advent of synthetic potent analgetics it became more difficult to describe these as a class without using some unwieldly descriptive phrase. Acheson and Pfeiffer have recently suggested that the term "opioid" be used in lieu of "synthetic opiate-like compounds." Accordingly, opioid is used throughout this text to describe compounds in this category.

The dosage of the various analgetics is a complex problem unless one considers the old maxim in medicine to the effect that in the treatment of symptoms of a disease one should always seek the minimal effective dose. Since pain is a symptom, it follows that the minimal effective dose should be used. The dosage is subject to variation because of factors such as age and clinical condition. Also, analgetic requirements will vary inter- and intra-individually. The greater the intensity of pain, the greater is the needed analgetic dose. It also follows that the more closely the dose meets the pain requirement, the lower the frequency and severity of undesirable reactions. In short, there is no substitute for good clinical judgement.

The search for synthetic analgetics to meet specific pain situations is carried on by a team of three: chemist, pharmacologist and physician. This joint effort is already successful to the extent that a sufficient number of potent opioids has been developed to make us independent of supplies of raw

opium as a source of potent analgetics. The chemists are making rapid advances in their knowledge of SAR (Structural-Activity-Relationships) and new chemicals having specific analgetic properties are constantly being invented. However, the extent to which current understanding of SAR is incomplete can be appreciated by this example: Codeine is the methoxy derivative of morphine. Levorphan is a close chemical analogue of morphine, yet its methoxy derivative does not have the same kind of biological properties as does codeine. Further, whereas codeine is a much weaker analgetic than morphine, the methoxy derivative of levorphan is almost as potent as the parent compound.

The pharmacologist has the task of defining the nature and extent of biological activity and assaying new chemicals for analgetic activity. A great variety of technics is available for the assay of compounds in animals. Generally, pain is produced by some easily measured means (such as thermal, electrical, chemical or mechanical stimulation) and the influence of the drug on the animal's *reaction* to these painful stimuli is measured. These procedures measure the reaction to the stimuli and not the subjective evaluation of pain as experienced in man. Laboratory technics are complex, time consuming and unsatisfactory in many ways, yet they do provide a rough screening process and more important, set the foundation for eventual trial in man. Although it is true that animal experimentation can suggest, but not accurately predict the effects of a drug in man, such studies are a most necessary prerequisite to human experimentation. They may, for example, reveal an unsuspected toxicity which would preclude the use of an experimental drug in man. Laboratory procedures are most effective in classifying compounds with a high degree of analgesia, such as morphine. Experience has demonstrated that any good technic in expert hands will yield results listing the opiates and

opioids in the same order of potency as is found in man. This is obviously most important since it is possible to compare an unknown with a standard, such as morphine, in animals and thus establish the dose to be used in the first trials in man. The study of analgetics in animals is least satisfactory when compounds of a low order of activity are assayed. The procedures in common use today are of little value in the determination of analgetic activity less than that produced by codeine.

The first trials of a new opioid in man can be carried out on either normal volunteers or patients with terminal carcinoma. In either case, ethical as well as scientific considerations must be taken into account. Patients with terminal carcinoma are not as satisfactory as volunteers for first trials because of many complicating factors. Among these are: possibility of impaired hepatic function, tolerance or addiction to other drugs, difficulties in quantitating the degree of pain and analgesia, and the problem of differentiating the untoward effects of the drug from the clinical signs arising from the patient's condition. In studies on human volunteers, artificially induced pain is produced by some measurable technic and the subjective pain threshold response is used to determine the intensity of analgesia. The two most common procedures are the Hardy-Wolff-Goodell technic and the electrical stimulation of tooth nerves. The Hardy-Wolff-Goodell procedure is based on the measurement of pain thresholds produced by focusing a heat lamp on the forehead of the subject. Although this technic is subject to criticism, it does yield results which are practical and useful particularly when studying the more potent opioids. The stimulation of teeth nerves is carried out by measuring pain thresholds induced by the carefully controlled application of an electrical current to a metallic filling in a tooth.

This procedure has been studied most carefully by Stanley Harris of Northwestern University Dental School and is particularly useful in the assay of materials with a low order of analgetic activity.

"Normal human volunteers" is a term sometimes humorously considered synonymous with "medical students." In our opinion a human volunteer is more than one who is informed of the hazards of the experiment; he should have the training and knowledge to make a *responsible* decision as to whether he wishes to volunteer. Thus, any medical student is not automatically qualified as a volunteer. The results obtained from studies of induced pain in man are generally misleading in at least two categories. First, the dose of an opioid tolerated by a volunteer is usually lower than that found useful clinically. Second, the incidence and severity of untoward reactions is higher in normal human volunteers. On the positive side, such experiments yield a much closer approximation of the clinical dose than does animal experimentation. Also, untoward drug effects, not discernible in animals may become apparent in such studies. As is true for clinical studies, the evaluation of any agent must be controlled carefully by the use of both a placebo and a standard drug without the observer or the subject knowing which drug has been administered.

The assay of analgetics under clinical conditions is the most difficult of all because it is the least readily controlled. Beecher and his associates in Boston have devised elaborate and strict methods of attacking this problem. Results comparable to those of Beecher can be obtained by utilizing very large numbers of patients with the application of multiple covarient statistical analysis to the data. In studying the drug effects on a symptom (pain) of a disease, all reliable investigations have these characteristics in common: placebo

or standard drug or both, both observer and subject are "blind," rigid criteria for selection and evaluation, and statistical analysis of the results.

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CHAPTER 2

SALICYLATES, PARAMINOPHENOLS AND PYRAZOLONS

SALICYLATES

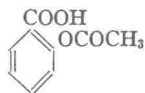
Chemistry

THESE DERIVATIVES of salicylic acid are divided into three classes: salts, esters of salicylic acid and salicylate esters of organic acids. Examples of these relationships are:

Salicylic Acid

(salt) Sodium Salicylate

(ester of salicylic acid) Methyl Salicylate



(salicylate ester of organic acid) Acetylsalicylic Acid (Aspirin)

The irritating properties of salicylic acid are such that its use is restricted to dermatology where its keratolytic action is desirable. It cannot be used systemically as the free acid; therefore, derivatives with more desirable properties than the parent compound were developed.

Pharmacology

Analgesia: The salicylates are much less potent analgetics than the opiates and opioids. They possess an advantage over these compounds in that they do not produce tolerance or addiction. The site of action of the salicylates is probably the optic thalami.

Absorption and Excretion: The salicylates are hydrolyzed to a limited extent in the gastro-intestinal tract and are rapidly absorbed. Absorption is also possible through any

mucous membrane and, under certain conditions, cutaneous absorption may occur. They appear in the body fluids and urine within fifteen minutes after administration and traces may be present for several days. About 20-40 per cent of salicylates are destroyed in the tissues and approximately one-fifth is found unchanged in the urine.

Other Properties: These compounds have a valuable antipyretic effect, indeed they were first developed as an economic necessity arising from the scarcity and high cost of quinine. They are useful in the treatment of gout, rheumatic fever and non-visceral pain situations. Increased urinary excretion of uric acid follows their administration. They are local irritants and some are still used for this effect. They are not sedatives and their weak bacteriostatic properties have no significance clinically. The salicylates have no effect on respiration except when given in toxic doses. The usual doses exert no effect on the cardiovascular system. The "anti-inflammatory" action of the salicylates, particularly their effectiveness in reducing swelling and inflammation of the joints in acute rheumatic fever, constitutes one of the chief indications for their clinical use.

Toxicity: The most common toxic manifestations to the usual doses of salicylates are referable to the gastrointestinal tract. Local gastric irritation is common and large doses may have a central emetic effect. Epigastric pain, nausea, emesis and diarrhea may result from the common doses. Sodium bicarbonate or other antacids will usually provide relief from these symptoms.

The salicylates will also lower prothrombin values and for this reason it is recommended that vitamin K be given to children where tonsillectomy is followed by the continuous administration of salicylates.

"Cinchonism" or "Salicylism" are the terms employed to describe mild salicylate intoxication. It resembles in many

ways the toxic reactions to quinine, particularly the visual and auditory symptoms. In addition to these signs and those listed above relating to the gastro-intestinal tract, other systems may be affected. Tachycardia, hyperpnea, central excitation (restlessness, delirium), fever, dermatitis and mucosal hemorrhage may occur. The treatment is symptomatic and the signs of toxicity usually dissipate rapidly when salicylates are withdrawn.

Severe salicylate intoxication presents some of the above signs first but these are rapidly followed by dyspnea similar to that seen in diabetic and renal acidosis. Central stimulation is displaced by depression and subsequently coma. Renal dysfunction occurs as evidenced by decreased output, uremia and, in some cases, nephritis. Respiratory failure with cardiovascular collapse immediately precedes death from salicylate poisoning. There is no specific treatment or antidote for severe salicylate intoxication. Treatment is purely symptomatic. Fluid replacement, support of the cardiovascular system, saline catharsis, reversal of central effects; all may have their place.

Indications

The salicylates are used as analgetic agents in neuralgia, myalgia, headache, dysmenorrhea, arthritis, etc. but are quite ineffective against deep visceral pain. They are often prescribed in combination with a pyrazolon or a paraminophenol. Codeine, caffeine, a sympathomimetic or a barbiturate is frequently contained in such combinations to good advantage.

Contraindications

The salicylates should never be given in the presence of severe renal disease. They should be used most cautiously in patients with a history of allergy, particularly asthma,

unless the history indicates to the contrary. Such individuals may display a hypersensitivity to these drugs, usually in the form of angioneurotic edema, asthma or anaphylactic phenomena. Epinephrine is sometimes but not always effective, and deaths have occurred as the result of salicylate ingestion by hypersensitive patients.

Salicylate Preparations

Sodium Salicylate, U.S.P., B.P.: The chemical structure of this salt of salicylic acid has been given. It is very soluble in water. The powder has a white or slightly pink color; it has a not unpleasant saline taste and is odorless. The usual dose for analgesia is 0.3 to 1.0 gram orally. In conditions such as rheumatic fever the dose may be increased to the point of maximum tolerance (about 4 gms per day).

Acetylsalicylic Acid, U.S.P., B.P.: (Aspirin) The chemical structure of this most commonly employed salicylate was given previously. It is sparingly soluble in water. The powder is white and odorless. It is not as irritating to the gastric mucosa as is sodium salicylate. The usual dose for analgesia is 0.3 to 1.0 gram orally.

Other Salicylates: The above two salicylates are the most commonly used for analgetic effect. Because there are at least several hundred proprietary and trade names of the salicylates and combinations of salicylates and other drugs, most of these will be listed in Table I.

PARAMINOPHENOLS

Chemistry

Acetanilid (antifebrine) and acetophenetidin (phenacetin) are classified as paraminophenol derivatives because both probably exert their pharmacologic effects after con-