Symposium on Pain: Part II

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Analgesic Drugs in the Management of Pain

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• **The use of potent narcotics to control severe pain should be of short duration and limited to patients with acute diseases or inoperable or metastatic cancer who require long-term relief. Continued and prolonged use of narcotics in patients with chronic benign pain is not recommended because of serious behavioral consequences, the development of tolerance, and addiction liability. Long-term use of analgesic drugs in chronic pain usually produces negative behavioral complications that are more difficult to manage than the pain it was desired to eliminate. The use of antidepressant drugs in the pain regimen has been found to provide increased relief of pain and often allows the dose of narcotic analgesic to be reduced or totally eliminated.**

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The most commonly employed method of managing pain involves the systemic administration of analgesic drugs. Analgesic drugs by definition act on the central nervous system to interfere with the development of negative affective responses, thus reducing or abolishing the integration of the pain experience. These effects are produced without necessarily producing unconsciousness. Drugs of other classes are useful singly or in combination with analgesics insofar as they can decrease fear, anxiety, and apprehension, promote sleep, reverse psychotic pain, or antagonize depression, especially depression intensified by chronic use of sedative-hypnotic drugs or opiates.

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Since analgesic drugs are only palliative, agents with specific therapeutic action are usually administered simultaneously. When properly administered, analgesics are very effective and have considerable advantages in simplicity of administration and low cost over many other procedures. Unfortunately, these desirable qualities are frequently responsible for imprecise application due to overuse or underuse of medication, the incorrect choice of drug or drugs, and choice of the wrong dosage. Two of the most common problems with analgesic drugs are undermedication in acute severe pain situations and overmedication in the treatment of chronic benign and especially chronic malignant disease.

BASIC CONSIDERATIONS

In approaching drug selection, physicians must differentiate disorders that are primarily traumatic (a burn or broken bone), pathophysiological (infection or inflammation), or psychological (perceptive or affective disorders, neurosis, or psychosis). Psychological problems rarely complicate the management of acute severe pain. However, in chronic recurrent benign pain or in any pain problem with repeated failure of the usual pain management techniques, psychological factors must be considered. Psychiatric evaluation or psychometric testing using an instrument such as the Minnesota Multiphasic Personality Inventory may provide information revealing a significant psychological factor. When this is evident or when pain complaints persist without demonstrable cause, the treatment of psychological problems in relation to pain behavior become paramount.

Affective changes induced by continuous opiate or sedative-hypnotic medications over many years should not be overlooked. The patient's continuing complaints about "pain" may be veiled requests for analgesics, sedative-hypnotic drugs, or minor tranquilizers, or for narcotic analgesics to support a drug dependence of which the patient may or may not be aware. Narcotic analgesics may partially compensate a patient; withdrawal of sedative-hypnotic drugs, minor tranquilizers, or opiates may reveal long-standing psychosis or neurotic behavior that presents itself as a request for the treatment of "pain."

Analgesic drugs can be divided into three groups: nonaddictive, moderately addictive, or strongly addictive agents. The choice of the optimal agent for a specific problem requires consideration of a great variety of factors, the most important of which are the quality, intensity, duration, and distribution of pain. In addition, some evaluation of the degree of anxiety and depression contributing to the pain complaint is of paramount importance.

The nonnarcotic or antipyretic analgesics may be useful in the control of mild pain such as headache, joint pain, neuralgia, and myalgesia. Some are especially effective when the treatment of rheumatic disorders is considered. When administered alone, these compounds are usually not effective in controlling moderate or severe pain and are not generally useful in managing pain arising from spasms of smooth muscle. As the intensity of pain increases, the use of codeine or other agents with relatively low addiction potential, singly or in combination with nonnarcotic analgesics, may be beneficial.

Severe pain usually requires therapy other than simple analgesic medication. Strongly addictive drugs are useful only when nonaddictive or moderately addictive drugs are ineffective and other forms of pain management cannot be used or are only partially effective. Early use of strong analgesics should be avoided, as too-early administration may mask symptoms and make diagnosis difficult during the duration of action of the drug. The narcotic analgesics are all strongly addictive, ie, repeated doses of 60 mg or more of morphine sulfate per day for 30 or more days are associated with the development of tolerance, physical dependence, and the possibility of withdrawal. However, these agents are considerably more effective than the weak or nonaddicting agents. They are useful for the pain associated with burns, trauma, deep structures, and musculoskeletal disorders. Intense pain, as in coronary occlusion, acute pancreatitis, and biliary or renal colic, often requires the appropriate use of these potent analgesic drugs.

Once an analgesic drug has been selected for use in a particular patient, it is necessary to determine optimal dosage. Optimal dosage may be defined as the minimal dose repeated often enough to produce the desired therapeutic effect while avoiding complicating side effects. Implicit in this description of optimal dosage is the need for continued observation of the patient in order to properly evaluate the relief of pain, provide for increased or decreased quantities of analgesic drug, and to discover undesirable side effects early. The proper evaluation of the results of analgesic therapy may require the help of the patient, attending nurses, and family.

An unfortunate but widespread practice is that of prescribing analgesic drugs and assuming, without proper follow-up, that patients derive relief because the amount and type of medication prescribed is adequate as described in the manufacturer's package insert. Most therapeutic failures with analgesic drugs may occur not because the patient is hypersensitive to the drug, has an idiosyncratic ability to fail to respond to the drug, or is psychoneurotic, but because the drugs and dosages chosen by the physician were inadequate for the job at hand. The fear of drug addiction and the attendant side effects of the drug, such as dizziness, nausea, and vomiting, have caused wary physicians to use so-called potentiating agents to minimize undesirable side effects and maximize analgesic drug responses.

Thus, in the treatment of acute pain, inadequate doses of narcotic analgesics have frequently been combined with phenothiazines, antihistamines, or minor tranquilizers in the belief that these would enhance analgesic response to low doses of narcotic analgesic agents to the point where they would provide "potentiated analgesia." Recent evidence suggests that the phenothiazines potentiate only the sedative action of the narcotic analgesic drugs and do not provide greater relief of pain. Indeed, some of the phenothiazine medications, such as promethazine hydrochloride, that are chosen for use as potentiators may have antianalgesic effects, and while they enhance sedation, they may actually increase the patient's discomfort.

NONADDICTIVE AGENTS

The nonaddictive agents include the salicylates, salicylamide, the analine derivatives, the phenylpyrazols, mefenamic acid and indomethacin, and a class of arylalkanoic acids such as ibuprofen and related agents. In clinically useful dosages, these compounds are without psychotropic activity except for changes in affective behavior concomitant with the relief of fever, inflammation, and pain. Although these drugs are widely abused, long-term use is not associated with the development of physical dependence and tolerance. Psychological dependence is not unknown, and is reinforced by frequent advertising that extols the virtues of buffered or unbuffered, soluble, effervescent, or insoluble products. The mechanisms by which these drugs produce analgesia are largely unknown, but evidence exists that they act peripherally on pain reception mechanisms, for instance by blocking the generation of impulses at chemoreceptor sites for pain in the skin (Table 1). Salicylate-like agents may affect prostaglandin mechanisms insofar as these are involved in pain modulation, inflammation, febrile response to bacterial pyrogens, and, perhaps, headaches of vascular origin. The great variety and over-the-counter availability of nonaddictive analgesic agents and the great volume of television promotional material, at times quite misleading, continue to confuse the public and even physicians about the properties of aspirin and other aspirin-like compounds. Since these agents can be obtained without prescription,

Table 1.—Analgesics and Other Drugs for Relief of Pain

Mechanisms of Interference With Pain	Type of Drug
Reversal of specific pathophysiologic events	
Infection	Antibiotics
Inflammation	Anti-inflammatory agents
Gout	Antihyperuricemic agents
Interference with specific chemical substance involved in pain reception peripherally	Antipyretic analgesics
Interference with conduction of pain away from affected site	Local anesthetics
Interference with CNS perception of pain and development of affective responses	Narcotic analgesics
Interference with anxiety, tension, or depression	Sedatives & hypnotics, phenothiazine tranquilizers, skeletal muscle relaxants, & antidepressants
Interference with consciousness	Anesthetics

toxicity frequently results. In addition, patients may be reluctant to accept these agents when prescribed for specific indications where reasonable expectations of positive therapeutic responses exist, simply because familiarity has bred contempt.

Acetylsalicylic Acid (Aspirin)

Aspirin is the most frequently used and extensively employed analgesic, antipyretic, and anti-inflammatory agent. It is as effective as and cheaper than proprietary drugs and has a relatively low incidence of side effects in the dosage range normally used. It is the prototype for other members of its class and is the standard of reference for therapeutic trials comparing and evaluating this type of agent. Physicians should consider the use of a new drug in this class only if its performance is equal to or greater than aspirin's analgesic efficacy while maintaining aspirin's low incidence of side effects. Controlled studies with patients in pain from varying causes have repeatedly shown that analgesia produced by aspirin in doses of 0.3 to 0.6 gm every four hours is superior to that produced by placebo medication.[1,2] Doses between 0.6 and 1.0 gm have recently been reported to produce an increase in peak analgesia, with somewhat prolonged analgesic action and little actual increase in side effects observed. The risk of higher doses of aspirin may be justified when aspirin is used for its antirheumatic properties. Administration of higher dosages is questionable when the drug is used for its analgesic properties alone in nonrheumatic pain problems.

Following oral ingestion, salicylates are absorbed in the stomach and upper intestine, resulting in appreciable plasma concentrations in 30 minutes or less, with peak concentrations at about two hours. The rate of absorption of aspirin is determined by a variety of factors, including the disintegration and dissolution rate of the oral formulation administered, the pH at mucosal surfaces, and the gastric emptying time. Despite widely publicized claims of one brand of aspirin reaching peak plasma levels quicker than others, there is little evidence equating pain relief with salicylate plasma levels. Salicylates are absorbed by passive diffusion of the nondissociated lipid-soluble molecule. The gastric mucosa and acid pH favors absorption by increasing the concentration of the nonionized form, but at the same time it decreases the solubility of solid tablets. Net absorption, therefore, is the result of the rate of dissolution of the tablet, the amount of nonionized drug present at the gastric mucosa, and the gastric emptying time.

Chronic use of aspirin or the use of large dosages may produce epigastric distress and sometimes painless gastrointestinal bleeding, especially in patients with peptic ulcers. Sensitivity to aspirin often appears in patients with asthma and allergy. Excessive doses produce salicylism consisting of tinnitis, headache and other mild mental effects, sweating, gastrointestinal disturbance, tachycardia, and tachypnea. These symptoms may progress from stupor, hyperthermia, hyperventilation, and changes in acid base and electrolyte balance, to coma, cardiovascular collapse, respiratory failure, and death.

Special Aspirin Preparations.—There is poor correlation between blood salicylate levels and analgesic effects. This has led to numerous attempts to modify the absorption and elimination of aspirin to produce earlier, greater, or more prolonged analgesia. Most of the studies comparing special aspirin formulations or other salicylates with aspirin have assayed only blood salicylate levels instead of overall analgesic effectiveness compared to blood salicylate levels, as would be required to make a valid comparison.[3,4] Blood salicylate levels, unfortunately, do not correlate well with analgesic effectiveness, particularly when simple salicylates are compared with aspirin-based mixtures.[1]

Comparison of plain aspirin with special aspirin preparations may also be confused by the crucial factor of bioavailability of the drug. Different preparations of aspirin may vary in the rate at which they deliver the drug in biologically useful form. This variability is further compounded by several factors: what physical state the tablet is in when it arrives in the stomach, whether the tablet was administered with or without water, whether the tablet was chewed or swallowed or had been dissolved in effervescent solution, how much food was present in the stomach, and whether salicylate was administered in an alkaline medium. Aspirin dissolved in water or in water containing alkali tends to decrease blood levels of unhydrolyzed aspirin as well as total salicylate; however, the presence of excess alkali and repeated administration of effervescent preparations may alkalinize the urine and cause an increase in salicylate clearance, thus decreasing plasma salicylate levels.

Buffered Aspirin.—Mixtures of aspirin and antacids were developed in attempts to enhance absorption and produce more rapid analgesia. Television promotional material for buffered aspirin claims that it acts faster than regular aspirin and induces less stomach irritation, but the clinical evidence is not very convincing that it has a more rapid

onset, greater peak analgesic action, or prolonged duration of analgesia than that of ordinary aspirin.[5-7] Carbaspirin calcium, which is the most soluble acetyl ester salicylic acid, is said to be more rapidly absorbed than aspirin; however, again, a well-controlled clinical study has not substantiated these claims. These results are not unexpected in view of the aforementioned factors of the influence of absorption and analgesic potency, and because of overall difficulty in clinically assessing potency and analgesic responses to this class of agents.

Enteric-Coated Aspirin.—This form of aspirin was introduced to prevent or reduce gastric irritation by delaying absorption of the drug until it reaches the small intestine, and thereby preventing the corrosive effects of salicylate crystals on gastric mucosa.[8] There are great differences in the rates at which these tablets pass through the stomach and are absorbed in the small intestine. Rate differences cause variable and, at times, unpredictable analgesic action.

Sustained-Release Aspirin.—Sustained-release aspirin was formulated to increase the duration of pain relief. However, the superiority of this form over standard aspirin preparations administered repeatedly at appropriate time intervals has not been adequately demonstrated.[9]

Aspirin Compounds.—Mixtures containing aspirin, phenacetin, and caffeine have long been popular because these drugs are thought to produce greater analgesia than aspirin alone. No data exists that impressively describes the superiority or inferiority of aspirin-phenacetin-caffeine-type compounds to aspirin in the majority of patients with pain. Thus, these mixtures have been called "irrational" analgesic mixtures by certain authors. One can look forward to the disappearance of a variety of these over-the-counter medications when deliberations currently being conducted by the Food and Drug Administration are completed and recommendations concerning "irrational" mixtures implemented.

Other Salicylates.—Sodium salicylate and salicylate choline are more soluble than aspirin and theoretically should act more rapidly. However, clinical trials have shown that they produce less satisfactory analgesia than aspirin and therefore have limited utility.[10] Salicylamide, which was synthesized over 100 years ago, recently has been advocated as a substitute for aspirin in patients with rheumatic fever and as an ingredient in analgesic mixtures. The analgesic and antirheumatic properties of this compound are not easily demonstrated after 0.6 gm.[5,11] One study reports favorable analgesia with doses of 2 gm every four to eight hours. However, these are dosages high enough to produce gastrointestinal and central nervous system side effects, including sedation.

In patients with moderate to severe pain, the drug does not seem to be more effective than placebo medication. Although salicylamide can be used safely in patients who are allergic to aspirin, other aspirin substitutes are probably more effective. At present, there seems to be little to support the use of this particular agent.

Paraminophenols (phenacetin, acetophenetidin) are often used as substitutes in patients who are allergic to salicylates or for some reason are unable to tolerate these compounds. The usual dose is 0.3 to 0.6 gm every three to four hours. Phenacetin is found in many headache powders sold without prescription and for this reason tends to be frequently misused. Toxicity occurs from ingestion of large amounts over long periods, and manifests as methemoglobinemia and sulfhemoglobinemia that cause cyanosis, dyspnea, weakness, and anginal pain.

Evidence suggests that phenacetin is comparable in potency to aspirin as an analgesic, but may be somewhat less potent as an antipyretic.[12] In a few instances, hemolytic anemia has been attributed to use of phenacetin.[13,14] This anemia may appear in chronic mild form after use of large doses of phenacetin, and seems to disappear on discontinuation of the drug. More rarely, acute severe hemolytic anemia may occur after a single dose of phenacetin in individuals with an inborn glucose 6-phosphate dehydrogenase abnormality. Even more rarely, the same reaction may occur as an allergy. Phenacetin does not appear to cause gastric blood loss in a manner similar to that of aspirin. A rare sensitivity reaction is skin rash. Many recent reports have linked excessive consumption of phenacetin containing analgesics with renal papillary necrosis.[15] Incontrovertible evidence that phenacetin causes nephropathy is lacking. Nevertheless, many clinicians have discontinued the use of phenacetin and phenacetin-containing compounds.

Acetaminophen has been reintroduced as a substitute for phenacetin because of the reduced incidence of methemoglobinemia and other toxic reactions. The usual dose of this compound is anywhere from 0.3 to 1.0 gm every three to four hours. Renal damage following the use of acetaminophen has not been reported, nor is this compound thought to cause gastrointestinal hemorrhage. Acetaminophen, therefore, is recommended as a long-term substitute for aspirin when the latter is contraindicated. The compound is approximately equipotent with aspirin as an analgesic and antipyretic. However, it is decidedly less effective than aspirin in rheumatoid arthritis and other inflammatory conditions.

Pyrazolones

Aminopyrine, a highly effective analgesic antipyretic and antirheumatic drug, has a reasonably high risk of agranulocytosis, making its routine use for chronic pain unjustifiable. Phenylbutazone, a congener of aminopyrine, relieves pain primarily by anti-inflammatory action. The dose varies, but 0.4 to 0.6 gm daily in three divided doses produces maximum benefit. The risk of toxicity is the same as that of aminopyrine; therefore, the drug should be restricted to short-term use not longer than one week for treating acute tendonitis, bursitis, and gout, and for tiding over patients with rheumatoid arthritis. In patients with rheumatoid spondylitis, phenylbutazone has provided effective maintenance in doses of 0.1 to 0.2 gm daily, less than half the amount needed for other conditions without toxicity.

Oxyphenbutazone, a metabolite of phenylbutazone, was

introduced as a compound having approximately equal analgesic efficacy but less toxicity than the parent compound. Unfortunately, this does not prove to be the case. The usual daily dosage of the compound is 0.3 to 0.4 gm divided into three or four doses. The patient receiving phenylbutazone or oxyphenbutazone must be closely monitored with frequent hematologic studies to properly determine the occurrence of serious side effects necessitating discontinuation of the agent. Because of the possibility of serious adverse effects and the lack of good evidence indicating superior analgesic potency, pyrazolones are rarely if ever indicated for general-purpose use in relief of pain.

Indomethacin

In terms of the analgesia produced in nonrheumatic pain, 50 mg of indomethacin has been found to be approximately comparable to 600 mg of aspirin. However, indomethacin is recommended exclusively as an anti-inflammatory agent in rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and gout. Long-term administration of this drug should be limited because of the substantial incidence of adverse effects on the central nervous system and the gastrointestinal tract. It should not, therefore be considered for use as a general-purpose analgesic. In the treatment of rheumatoid arthritis, its intended purpose, results have been somewhat disappointing. The drug has been found to be more effective than salicylates in relieving pain of osteoarthritis of the hip and other peripheral joints, acute gouty attacks, spinal osteoarthritis, and rheumatoid spondylitis. Patients should be started on a regimen of 50 to 75 mg per day and dosages increased until side effects appear.

Carbamazepine

Carbamazepine represents a major advance in the treatment of trigeminal neuralgia, glossopharyngeal neuralgia, and other central pain states. The usual starting dose is 100 mg twice daily, increasing the dosage until relief is achieved. Care should be observed as the dose approaches 1 gm/day. The drug is not useful for relieving other types of pain, and carries a small risk of serious hematopoietic side effects. While depression of the white blood cell count has been infrequently observed, in a recent clinical trial of carbamazepine as an antiepileptic agent, agranulocytosis was not observed and hematopoietic side effects were not serious enough to discontinue use in any of the 47 patients in whom the drug was being evaluated. Carbamazepine, therefore should be used for central pain states such as those described, and the patient should be examined frequently for side effects.

In patients who do not tolerate carbamazepine well, phenytoin may relieve the pain of tic douloureux or other central pain states. In addition to carbamazepine or phenytoin, one may use the combination of amitriptyline hydrochloride and fluphenazine hydrochloride. The amitriptyline hydrochloride is started at 25 mg three times a day and increased to a total of 100 or 150 mg per day. The fluphenazine hydrochloride is started at 1 mg once or twice a day and increased to somewhere between 5 and 6 mg/day.

Ibuprofen

Ibuprofen, a phenylproprionic acid derivative, has been marketed in the United States for the last year or so. In recommended dosage, its anti-inflammatory effects in rheumatoid arthritis are less than those provided by full doses of aspirin. At low dosages, ibuprofen is analgesic, but seemingly without anti-inflammatory effect. Compared with aspirin, complaints of gastrointestinal distress are reduced and occult bleeding is diminished. Exacerbation of peptic ulcer has been reported and headache and alterations in hepatic function tests have been noted. Visual field defects and decreased visual acuity have been reported. The recommended dose for the symptomatic treatment of rheumatoid arthritis is 900 to 1,600 mg/day. Because the drug is expensive and its efficacy and safety for long-term therapy are still incompletely established, it cannot be recommended as a substitute for aspirin in the routine management of chronic pain. Other drugs related to ibuprofen have very recently appeared on the market, and the safety and efficacy of this new class of agents will be evaluated through clinical experience within the next few years.

WEAK NARCOTIC AGENTS WITH LOW ADDICTION POTENTIAL

Codeine

If one excludes aspirin, codeine is the most widely used oral analgesic and is generally accepted as the standard of comparison for the drugs in its category. Prolonged use of codeine in the dose of 65 mg or more every four to six hours for several months is associated with relatively little risk of significance of narcotic dependence. Tolerance does develop, however, requiring an increase in dosage to provide continuing relief. The incidence of codeine abuse among addicts is relatively small, as is the incidence of serious side effects from the drug. The low incidence of abuse should be contrasted with the frequent use and easy availability of the drug in order to dispel addiction-abuse fears.

Codeine is capable of producing all the adverse effects characteristic of narcotic analgesic drugs, including nausea, vomiting, sedation, and dizziness. These effects are more often observed in ambulatory patients than in those confined to bed. Although 60 mg of codeine can measurably depress respiration, the degree of depression is of little clinical significance. A relatively small incidence of serious side effects, together with low cost, makes codeine superior to other analgesics with low addiction potential. This drug is recommended in preference to new, relatively untested drugs for the treatment of moderate pain that shows minimal response to nonaddictive agents.

Propoxyphene

Propoxyphene has enjoyed widespread popularity because it is said to have the same analgesic potency as codeine without addiction potential and without signifi-

cantly lower incidence of undesirable side effects. Recent clinical trials have suggested that this product is difficult to distinguish from placebo in analgesic potency.[18] This information is somewhat surprising, considering propoxyphene's great popularity in recent years. Administration of propoxyphene in dosages of 65 mg four times a day for several months does not produce drug dependence; however, larger doses (600 to 825 mg of the drug daily for eight weeks) can cause a slight but significant abstinence syndrome on withdrawal. Dosages up to 2.4 gm/day have been associated with a significant incidence of withdrawal symptoms. Propoxyphene, 32 mg or 65 mg, is also available in compounds with 227 mg of aspirin, 162 mg of phenacetin, 32.4 mg of caffeine, and 50 mg of propoxyphene napsylate in combination with 325 mg of acetaminophen.

Although propoxyphene has been classed as nonaddictive and does not come under the preview of narcotics laws, dependence may occur with repeated administration in higher dosage. In view of these considerations and the greater cost of the drug than that of aspirin and codeine, as well as the lack of convincing evidence of superior analgesic potency, there seems to be little to recommend the drug for routine use. Propoxyphene may be useful for patients with moderate pain who are unable to tolerate codeine-aspirin combinations, and acetaminophen may be useful for patients who do not tolerate aspirin very well.

Pentazocine

Pentazocine, a benzomorphan derivative with opioid antagonist action, is a relatively new analgesic that has been widely used because it can be taken orally. It is said to be devoid of addiction potential and produces fewer side effects than other narcotics. Oral doses of 50 mg are about equivalent to 60 mg of codeine. Side effects have been reported to occur. These include increases in blood pressure and heart rate, sweating, dizziness, light-headedness, nausea, and respiratory depression. Although the incidence of physical dependence is less with pentazocine than with other narcotics, reports of pentazocine dependence have been numerous. Among patients with chronic pain seen at the University of Washington pain clinic, the incidence of pentazocine addiction is low, but self-administration of doses up to 3,000 mg/day has been observed. Despite these potential shortcomings, pentazocine constitutes an important addition in the pharmacologic armamentarium and for the relief of pain.

This drug should be used with caution in patients who have received high doses of potent narcotic analgesics administered for long periods of time that are acting during the time of an intended course of (pentazocine) therapy.

POTENT NARCOTIC AGENTS WITH HIGH ADDICTION POTENTIAL

Morphine and Related Compounds

The beneficial actions of morphine in the treatment of refractory intense pain are well known. Significant disadvantages and undesirable side effects complicate the management of pain with this and related drugs. Many of the actions of morphine on the central nervous system can be classified as adverse. Unwanted sedation, mental clouding, inability to concentrate, lethargy, impairment of mental or physical performance or both, constipation, nausea and vomiting, tolerance, physical dependence, and suppression of cough may occur. These may or may not be desirable concomitants of analgesia with this drug, depending on the setting as well as the reasons for which the drug is used. In a chronic pain patient who could otherwise maintain a normal life-style, impairment of mental and physical performance is an undesirable action. In terms of the fearful, apprehensive patient who is about to undergo surgery, general impairment of mental and physical performance may be a useful adjunct and the reason for preanesthetic medication.

Affective changes produced by morphine are not always perceived as pleasant; some patients experience untoward reaction such as anxiety, fear, or dysphoria. Nausea and vomiting frequently occur. Dizziness, respiratory depression, and constipation are among the most common adverse effects. The development of tolerance and physical dependence and the spectre of uncomfortable withdrawal limit the utility of this agent for long-term management. For these and other reasons, the search for more effective analgesic agents with fewer side effects has continued, developing a varied group of strong analgesic drugs (Table 2).

The differences between morphine and its semisynthetic and synthetic related agents have been overestimated. The recent crisis produced by increased heroin abuse tends to reinforce the unbiased belief that one opioid is more analgesic or euphoriant or both than another. In equal analgesic doses, most of the agents in Table 2 produce approximately the same incidence or degree of unwanted side effects, including euphoria. However, some patients may exhibit side effects with one drug and no side effects or different side effects with another. For these reasons, morphine surrogates are useful and a welcome addition to the fight against pain.

Pain that does not respond to oral administration of codeine with or without aspirin should be evaluated for possible treatment with an opioid drug. The management of severe intractable pain due to inoperable or recurring cancer becomes an exacting exercise involving a succession of therapeutic agents to maintain the patient in comfort. Physical dependence and tolerance occur whenever a narcotic is given in therapeutic dosages under these conditions. But, in patients with a painful terminal illness, concern about addiction should be set aside in favor of fulfilling the primary obligation to ease the pain. In this situation, however, patients are likely to receive more medication than is commensurate with integration of personality, maintaining relationships with the family, and keeping whatever level of function is desired by the patient. One must be conservative, keeping the amount of opiate analgesic as low as is consistent with pain relief. Very helpful in this regard is the use of local or regional nerve conduction block with local anesthetic agents.

Thus, with these and other behavioral techniques, doses

Table 2.—Potent, Highly Addictive Analgesic Drugs

Generic Name	Trademark	Approximate Adult Dose (mg)	Duration of Action (hr)	Abuse Liability
Morphine and Its Congeners				
Morphine	...	10	4-5	Relatively high
Papaveretum	Pantopon, Omnopon	15	4-5	Relatively high
Hydromorphone hydrochloride	Dilaudid, Hymorphan	1.5	4-5	Similar to morphine
Oxymorphone hydrochloride	Numorphan	1-1.5	4-5	Similar to morphine
Metopon hydrochloride	...	3-3.5	4-5	Similar to morphine
Heroin	...	3	3-4	Similar to morphine
Nalorphine hydrochloride (antagonist)*	Nalline	10-15	...	None
Naloxone hydrochloride (antagonist)†	Narcan	...	...	None
Synthetic Analgesics of the Morphinan Series				
Racemorphan hydrobromide	Dromoran	5	4-5	Similar to morphine
Levorphanol tartrate	Levo-Dromoran	2-3	4-5	Similar to morphine
Dextromethorphan hydrobromide‡	Many cough mixtures	...	...	None
Levallorphan tartrate‡	Lorfan	...	...	None
Synthetic Analgesics of the Benzomorphan Series				
Phenazocine hydrobromide	Prinadol	2-4	4-5	Similar to morphine
Pentazocine	Talwin	45-60	2-3	Substantially less than morphine
Cyclazocine	Not available	0.3	4-5	None
Synthetic Analgesics of the Phenylpiperidine (Meperidine) Series				
Meperidine hydrochloride	Demerol	50-100	2-4	Similar to morphine
Anileridine hydrochloride	Leritine	25-35	2-3	Similar to morphine
Piminodine esylate	Alvodine ethanesulfonate	7.5-10	2-4	Similar to morphine
Alphaprodine hydrochloride	Nisentil	50	Very short	Similar to morphine
Synthetic Analgesics of the Diphenylpropylamine (Methadone) Series				
Methadone hydrochloride	Dolophine, Adanon, Althose, Amidone, Westadone	10	4-5§	Similar to morphine
Dipipanone hydrochloride	Pipadone (British)	20-25	4-5	Similar to morphine
Dextromoramide tartrate	Palfium, Dimorlin	6	4-5	Similar to morphine
Fentanyl citrate	Sublimaze	0.2	4-5	Similar to morphine
Phenothiazines				
Methotrimeprazine	Levoprome	15-20	4-5	None

*Not used for analgesia.
†No analgesic activity.
‡Very little analgesic activity at any dose.
§Single dose: longer in tolerant individuals.

of narcotic drugs can be kept low as long as possible. Narcotics should be reserved until nonnarcotic drugs, other drugs, and other types of therapy no longer provide adequate relief.

Percodan

Percodan, a mixture containing oxycodone hydrochloride and homatropine aspirin, phenacetin, and caffeine, is a synthetic narcotic analgesic related to dihydrocodeinone and is subject to control under federal narcotic regulations. As an analgesic, 10 to 15 mg of Percodan postoperatively is the equivalent of 10 mg of morphine intramuscularly or 120 mg of codeine postoperatively. After oral administration, the analgesic effect begins within 10 to 15 minutes, peaks at 45 minutes, and persists for three to six hours. The drug is useful in moderate to severe pain arising from bursitis, injuries, dislocation, fractures, neuralgia, and postoperative and postpartum pain. Side effects may include dizziness, headache, weakness, nausea, vomiting, and constipation. Urticaria and rash have been observed in patients who are hypersensitive to other opium alkaloids. Cardiac and respiratory depression observed are comparable to that seen after codeine. The incidence of side effects is somewhat lower than that seen after comparable doses of morphine.

The tolerance and addiction potential of Percodan was reported by the manufacturer to be less than that of morphine, yet greater than that of codeine. The drug efficacy study of the National Academy of Sciences National Research Council considered the addiction potential of Percodan to be equivalent to that of morphine. We find the risk of addiction greater than that attributed to morphine for the following reasons: oxycodone hydrochloride, a synthetic codeine derivative, is compounded with aspirin, phenacetin, caffeine, and homatropine and is promoted by the manufacturer as an aspirin-phenacetin-caffeine with codeine equivalent but without the codeine. This practice leads the physician to prescribe Percodan as freely as he did other aspirin-phenacetin-caffeine with codeine formulations. In terms of analgesic response and patient acceptance, Percodan should be thought of as an effective, orally active morphine-like agent with fewer side effects than morphine, but with equal addiction liability. Although true addiction to codeine in patients with pain is relatively rare, addiction to Percodan has been observed with some regularity at the pain clinic of the University of Washington Hospital in Seattle.

Although no evidence exists suggesting that Percodan

provides a therapeutic advantage sufficient to offset its abuse or addiction potential, the drug is a useful, orally active medication, especially for acute transient pain relief. Since it is our belief that short-acting pain medications are not justifiable for continued use in chronic pain situations, we cannot recommend that the use of Percodan be continued past the initial phases of treatment for pain. Percodan, though useful, cannot be recommended as a drug of choice.

Percodan is best considered as orally administered active morphine and should not be dispensed as freely as if it were codeine.

Management of Narcotic Dependence With Methadone Hydrochloride

In addition to its efficacy as an oral analgesic in managing chronic pain, methadone hydrochloride provides unique benefits in addicted patients in whom a narcotic is to be withdrawn. It is also quite useful for the treatment of terminal cancer pain patients in that it is easy to reduce the dosage to that providing reasonable pain relief and improved psychological function while attending to the unmasked pain by use of a local anesthetic block. At times, the prudent use of tricyclic antidepressant drugs is helpful in further selection of narcotic dosage.

The method for methadone substitution-withdrawal is fairly simple. The patient is observed and if significant withdrawal symptoms appear, 15 to 20 mg of methadone hydrochloride is given orally. The patient is evaluated at the end of four hours, and if withdrawal symptoms are still present or exacerbated, an additional 15 to 20 mg is given orally. After four hours, the procedure may be repeated at four hourly intervals until the patient is free of withdrawal symptoms.

Once the patient has been free of withdrawal symptoms for 24 to 36 hours, programmed detoxification can begin. The stabilization dose can easily be calculated by totalling the number of milligrams of methadone required over a 24-hour period to keep the patient free of withdrawal symptoms. This amount may be given as a single oral dosage or may be divided and given at intervals each day. One can also approximate the amount of the stabilization dose from the patient's medical record. Usually, 10 mg of morphine sulfate, 75 to 100 mg of meperidine hydrochloride and 2 mg of hydromorphone hydrochloride require substitution of 7.5 to 10 mg of methadone hydrochloride postoperatively.

In patients who remain free of withdrawal symptoms for a 24-hour period on a stabilization dose of methadone, 20% of the daily dosage can be omitted each succeeding day until the patient receives no more. Should the patient have adverse responses to such a rapid reduction of dosage, a lesser percentage may be chosen. Although rhinorrhea and mild withdrawal symptoms may develop, this method completely avoids the usual agitated withdrawal and allows safe detoxification of even the most severely ill patient. Narcotic addicts in whom the narcotic is not to be withdrawn can be maintained free of withdrawal symptoms by maintenance doses of methadone.

Although methadone maintenance is still experimental in the United States, its efficacy has been established and its benefits clearly outweigh its hazards. However, it should be emphasized that the maximum benefit from this kind of therapy can be obtained only in a setting in which adequate psychiatric, social, and vocational programs provide a sound therapeutic milieu specifically appropriate to the needs of the street addict. The use of methadone maintenance in a narcotic addict is not without philosophical as well as legal problems if the physician does not have adequate time to provide the other necessary components of an adequate and appropriate program for these people.

OTHER DRUGS

In addition to analgesic drugs, sedative-hypnotic, antianxiety, antidepressant, and tranquilizer medications may be of use. The blockade of depression and anxiety can alter patient's interpretation of painful stimuli as well as produce alterations in behavior. Sedative-hypnotic and antianxiety agents are associated with the development of tolerance and physical dependence. Chronic use and addiction to these agents may increase pain behavior in a given situation. Frequently, detoxification from sedative-hypnotic and antianxiety drugs is required to improve the patient's affect and provide better control of pain. A list of drugs and appropriate relative potencies for substitutions, stabilization, and withdrawal using phenobarbital as a long-acting agent during detoxification is found in Table 3. One must be cautious in correctly estimating tolerance for each patient and providing enough substituted phenobarbital to prevent agitation and the occasional fatal grand mal withdrawal seizure and yet not subject the patient to overdose.

The method of estimating tolerance is simply to provide 200 mg of pentobarbital orally, repeated at 2½-hour intervals until the patient shows nystagmus, slurred speech, or sleep. Using the estimated relative potency table (Table 3), one gives phenobarbital postoperative at 30 mg/day/100 mg of pentobarbital, used to produce sleep. The total dosage of phenobarbital so calculated may be given in divided doses over a day when tolerance of 300 to 500 mg of pentobarbital is determined and the danger of seizure activity and the relative necessity of substitution therapy is relatively low (10%). At doses above 1 gm of pentobarbital, the incidence of seizures during withdrawal is close to 100%.

Table 3.—Equivalent Dosages of Some Secative-Hypnotic Drugs and Phenobarbital

Generic Name	Postoperative Dose
Secobarbital	100 mg
Pentobarbital	100 mg
Diazepam	10 mg
Chlordiazepoxide	25 mg
Meprobamate	400 mg
Most barbiturates	100 mg
Glutethimide	500 mg
Whiskey	3-4 oz
Phenobarbital	30 mg

Nonbarbiturate Sedative and Antianxiety Agents

Frequently, patients undergoing detoxification procedures require sedation and antianxiety medication. The usual antianxiety medication, diazepam, has been finding less and less favor in the management of chronic pain. It appears to intoxicate the patient rather than to reduce anxiety. Tolerance and physical dependence seem to be a frequent problem in chronic pain patients. Withdrawal from diazepam is rarely expressed as hyperexcitability and seizures. However, the patient may become emotionally labile, insomniac, anorexic, and quite jittery. In addition there is evidence that most sedative hypnotics are hypoalgesic: that is, they actually increase the intensity of pain.

Recently, hyperalgesic properties for meprobamate have been described. Chronic use of sedative hypnotic drugs such as diazepam, meprobamate, or any of the short-acting barbiturates has been observed to intensify depression in chronic pain patients who are depressed because of the chronicity of their pain problem. The detoxification procedure described above seems to rapidly reverse that depression, producing elevation of mood and personality changes within the first four or five days of the detoxification procedure. The use of tricyclic antidepressants, ie, doxepin hydrochloride, helps this picture considerably.

Frequently, patients undergoing detoxification procedures require sedation and antianxiety medication. However, the use of any of the agents listed in Table 3 is inappropriate, since they are members of the same class of drug and will prolong the detoxification procedure. Thus, diphenhydramine or hydroxyzine hydrochloride may be used to provide sedation and even sleep. Given every four hours, 50 mg of hydroxyzine hydrochloride will decrease the patient's anxiety and improve his tolerance to the withdrawal procedures; 100 mg administered postoperatively may be used to induce sleep. As mentioned, these drugs are especially useful during detoxification from sedative-hypnotic drugs where barbiturates or substances that have cross-tolerance to barbiturates cannot be used without complicating the detoxification procedure.

COMMENT

Most patients with mild pain can be made comfortable with plain aspirin. Special aspirin preparations or other proprietary mixtures are little better than aspirin and are more costly. Their use should be reserved for patients who cannot tolerate aspirin.

Patients with moderate pain who do not respond to the nonaddictive analgesics usually derive sufficient benefit from aspirin compounded with small amounts of codeine or an agent of similar potency. The new, low-addiction-potential analgesics are more expensive and not demonstrably superior to codeine, and therefore should be reserved for patients who tolerate codeine poorly. The use of narcotic analgesics should be reserved for patients in acute, severe, intense pain. For chronic benign pain, the use of narcotic analgesic drugs for periods longer than four to six weeks will frequently produce problems of intensification of depression, habituation, tolerance, physical dependence, and fear of withdrawal, and may lead patients back to the physician's office with complaints of "chronic pain."

Nonproprietary Names and Trademarks of Drugs

Amitriptyline hydrochloride—*Elavil.*
Carbamazepine—*Tegretol.*
Carbaspirin calcium—*Calurin.*
Dextromoramide tartrate—*Palfium, Dimorlin.*
Doxepin hydrochloride—*Adapin, Curatin, Sinequan.*
Ibuprofen—*Motrin.*
Mefenamic acid—*Ponstan, Ponstel.*
Phenazocine hydrobromide—*Prinadol.*
Racemorphan hydrobromide—*Dromoran.*
Salicylate choline—*Arthropan.*

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