INTRODUCTION

Pain alleviation in infants and children has long been minimal, if not totally ignored. In recent years there at last has been a growing realization of the need for controlling pain in the young (Anand and Hickey, 1987; McGrath and Unrah, 1987; Ross and Ross, 1988; Schecter, 1989; P.A. McGrath, 1990), but the pain of burned children has received almost no attention (Perry and Heidrich, 1982). However, the extreme pain often experienced by children with burn injuries has led us to seek better means of managing pain in this group.

The Assessment of Pain in the Burned Child and Associated Studies in the Laboratory Rat

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CLINICAL STUDIES

Methods

In order to evaluate analgesic regimens, we needed a method of assessing the degree of discomfort in a given burned patient. This presented a problem, since at the time (1982) there had been no methods reported for pain measurement in children save one that gave a single overall result (Hester, 1979). Our intent was to determine the extent of pain during burn dressing changes (BDC). BDC occurs at least twice each day and lasts up to 3 hours. It is a time of severe distress for a burn patient. Since pain levels during this undertaking vary with ongoing procedures, a system for capturing these rapid fluctuations was needed.

The most sensitive instrument used in studies of adult pain is probably the visual analogue scale—a horizontal or vertical line bounded by no pain at one end and the most severe pain on the other. The patient marks a point on the line proportionate to his or her discomfort. Burned children, however, often have bandages on their hands and, in addition, those with extensive injuries are surrounded by a tent of heavy plastic (bacteria-controlled nursing unit) to reduce the chance of infection. In our search for an appropriate device we turned to formerly burned patients returning to the Shriners Burns Institute for reconstructive surgery. Seven different scales were presented to 17 subjects, all of whom recalled vividly the pain they had experienced during BDC at the acute phase of their burns. When asked with which scale it would have been easiest to convey the degrees of pain experienced in a BDC, the almost unanimous choice was a numerical rating scale from zero (no pain) to 10 (pain as bad as it could be). Encouraged by the agreement among subjects we compared this thermometer-like scale (TS) to a conventional zero to four verbal rating scale (“no pain” to “the worst possible pain”) similar to those used in most research on adult pain. In a study of postoperative pain in a group of 12 patients returning for plastic surgery, scores from the two scales agreed well (r=0.89, p<0.001). The TS, however, appeared more sensitive, since it clearly distinguished the onset and duration of analgesia.

To make the TS easily seen by acutely burned patients confined to bacteria controlled nursing units, we enlarged the scale to 77 x 18.7 cm (about 30 x 7 inches), with large white numbers on a crimson background, as red is the color that children most often associate with pain (Scott, 1978; Savedra et al., 1982).

Although the TS had worked well for assessing relatively steady postsurgical pain, the real test was whether it would succeed in estimating the varying pain of a BDC, a time of tension and stress for both the patient and attending burn nurses. The first trials were made with a 15-year-old boy whose burns covered 65 percent of his body surface area (he and his parents, as well as a witness and a pediatrician acting as the patient’s advocate, had signed a human studies consent form). The observer, whose task was to record all scores along with the accompanying BDC activity and the patient’s comments, was immediately struck by the willingness of the subject to give pain scores throughout the 2 hour BDC. It was at once apparent, however, that the chosen interval for obtaining scores (5 minutes) was much too long. In the second trial, therefore, the patient was asked for a score once each minute and requested to volunteer any changes that occurred between the moment to moment queries. This scheme worked well and has been followed in all subsequent studies (a mean pain score for the entire BDC is obtained from an average of scores obtained at times of actual BDC activity). The “dry-runs” with the original subject were continued over many weeks, and it was gratifying to see that as the wounds healed, the mean pain scores for the BDC fell to almost negligible levels.

Clinical Studies

We then began our first formal study, an assessment of pain and plasma β-endorphin (BEP) levels in 15 children between the ages of eight and 17, during 33 BDCs (Szyfelbein et al., 1985a). β-endorphin, an endogenous opioid, was expected to reflect the degree of stress in a given child and thus might serve as an index of pain for those unable to speak, such as infants and children being artificially ventilated. Unexpectedly, BEP on a given day was inversely proportional to the mean pain score of a BDC; that is, the higher the BEP level the less the pain experienced (Figure 1). Also of note was the finding that mean pain scores were directly related to the extent of burn injuries and indirectly related to body weight. These two variables combined in a multiple linear regression equation had a predictive power equivalent to that of BEP alone. In our current state of knowledge, we view these results as indicative of global arousal that leads to stress-induced analgesia (SIA). In keeping with other instances, SIA depends predominately on one particular type of opioid receptor, termed mu. We are currently investigating whether the use of an analgesic that acts on another distinct opioid receptor, called kappa, might offer better pain relief in the burned patient, since it involves different neural pathways that may well be more specific to burn pain.

The TS has since been used to further document that the amount of pain in a BDC varies directly with the extent of the burn injury (Atchison et al., in press). In addition, the TS shows that contrary to the widely held belief that third degree burns cause little or no pain because nerve endings are destroyed, third degree burns actually cause high levels of pain. The TS has also been used to determine the efficacy of drugs used for BDC (Szyfelbein et al., 1985b) and in addition has become the standard tool for evaluating
pain in all patients in this institution able to give scores (Osgood and Szyfelbein, 1989).

The plight of those on respirators or those too young to speak or understand numerical scales presents a far more difficult hurdle. Although in recent times a number of systems for pain assessment in the very young have been reported (Craig et al., 1984; Jay and Elliot, 1984; P.A. McGrath et al., 1985; Beyer and Aradine, 1987) there are as yet no widely accepted procedures for pain evaluation in this group (Schecter, 1989). For the most part these methods are based on behavioral observations. In some, for example, the “CHEOPS” (Children’s Hospital of Eastern Ontario Pain Scale), which rates the degree of particular behaviors, is used (P.J. McGrath et al., 1985).

We are presently working on a method for the assessment of pain in infants and toddlers that combines both physiological variables such as blood pressure, respiration, and heart rate, with behavioral measures. The goal is to develop a simple means of evaluation that has both validity and interrater reliability.

The most vexing dilemma, however, is the infant who is placed on a respirator to assist his or her breathing and is given a muscle relaxant to improve the efficiency of the machine. Thus paralyzed, the child is unable to convey any sign of discomfort or anxiety. The only recourse is to pay close attention to the monitors that continuously measure arterial blood pressure, respiration, and heart rate in all such patients. Although elevations of the vital signs are not unequivocal evidence of pain, they often return to normal levels following administration of an analgesic, and the onset and duration of effects of a particular drug correspond as expected. Thus effective pain management in the burned child can be difficult, but further studies designed to elucidate these problems should help to bring better pain control to this group.

LABORATORY STUDIES

At the turn of the century few survived even small burns (less than about 20 percent of the body surface area) while today the mortality level of all burned victims has fallen to approximately five percent (Burke, 1990). Without animal experimentation this achievement would surely have been unattainable. To define the underlying immense complexities of the pathophysiology of burns requires carefully controlled experiments that may lead to new or improved therapies in patients. Although clinical research is essential, fundamental work in the laboratory is also vital to progress in burn care.

Methods

To investigate basic mechanisms of pain and to address questions that cannot be resolved in the clinical setting, we depend upon the laboratory rat. In addition, the use of rat models allows studies to be conducted in the ab-
sence of many possibly confounding variables found in the clinic such as the presence of a multiplicity of drugs, frequent surgical procedures, age, and varying times after injury. In addition, analgesic drugs untied in burn victims can first be characterized in the rat. It is unfortunate that there is, as yet, no way to study the effects of burn injury on physiological and pharmacological processes except by subjecting an animal to this trauma. We have, in fact, tried without success to replicate results of the endocrine effects of burns in rats exposed to warm (37°C) or cold (4°C) environments (Osgood et al., 1986a; Osgood et al., 1990).

The rat burn model is a long established, and until recent times, a widely accepted procedure for establishing an organism’s response to burn injuries. At present, however, although animal care oversight committees recognize the necessity for such experiments, the activities and rhetoric of the animal rights movement appears to be intimidating and threatening to the editorial boards of many scientific journals. Nonetheless, the immense strides in the treatment of burns made over the past decades would have been impossible without animal models that have included dogs, guinea pigs, sheep, and particularly, laboratory rats. The underlying mechanisms of the alterations that occur in the dermal vasculature after burns and their relevance to burn wound healing (Ehrlich et al., 1987) have in large measure depended on the rat model. Marked reduction in the phagocytic activity of the reticuloendothelial system after burn trauma has also been demonstrated in this model. This finding helps to explain the sepsis that often occurs in patients with burns (Trop et al., 1989). Burn injury in the rat increases nicotinic acetylcholine receptors, and this may largely account for the marked elevation in the doses required for muscle relaxation with curare-like drugs after burns (Kim et al., 1988). The mouse model for burn injuries has been shown to exhibit similar changes in neuromuscular function, although these appear to have no relationship to the hypermetabolic and immunosuppressive responses that generally follow burn injury (Tomera et al., 1988).

That the rodent continues to play an important role in the progress of burn research is clearly brought out in the proceedings of a recent National Institutes of Health conference on trauma and burn injury (1990). This model has been selected for many studies, including investigations of the hypermetabolic response (Wood et al., 1990), local skin and distant lung injuries induced by second degree burns (Ward and Till, 1990), the regulatory role of T-lymphocytes in wound healing (Barbul and Regan, 1990), and the effects of burns on renal function (Aikawa et al., 1990). These investigations are but a few examples of a substantial body of work that has contributed to advances in the management of burns and increased survival among burn victims.

No investigator views the burning procedure with equanimity. However, the realization that research in animals with burns may help to reduce the suffering and enhance the recovery of young human burn victims well justifies this work. Frequent association with these children continually reinforces this conviction. The rat, unlike its human counterpart, is completely anesthetized while the burn is inflicted and after receiving intravenous fluids, is placed on a heating pad, in a box with fresh wood shavings until the time of the experiment. After waking, the rats show no evidence of pain, which is in keeping with our findings in patients who between therapeutic interventions such as dressing changes and physical therapy have low levels of pain (Szyfelbein et al., 1985a). Baseline sensitivity to pain at 2 days post burn when most studies are performed, is the same in burned and sham-burned (control) rats. When an experiment is completed all rats are killed with an overdose of barbiturates.

Two different tests are used to test antinociception (analgesia): tail-pinch and tail-flick latency. These standard procedures are employed because there is no feasible way to assess burn pain without involving the burn wound, a far more aversive stimulus than the brief discomfort of the tail-flick or pinch procedures.

Tail-flick latency is a spinal reflex that measures the time it takes a rat to "flick" its tail away from a beam of incandescent light focused on the distal portion of its tail (D’amour and Smith, 1941). In our laboratory, baseline latency is between 2 and 3 seconds, and the lamp automatically turns off at 7 seconds. For tail-pinch latency a hardwood clothespin is placed on the base of the tail and
LABORATORY STUDIES

Although we had followed variations in plasma \(\beta\)-endorphin levels in acutely burned children, sometimes over a period of months (Osgood et al., 1986b), the immediate effect of burns on this endogenous opioid remained unknown because of the unavoidable delay before a patient's hospitalization. Therefore, initial levels of peripheral \(\beta\)-endorphin following burn injury and its possible influence on pain perception were measured in a rat model with scald burn injury. There were marked increases in \(\beta\)-endorphin, as well as decreases in pain response in the rat, both in direct proportion to the extent of injury (Figure 2). This stress-induced analgesia (SIA) was prevented by the long-acting opioid antagonist naltrexone, suggesting that it was opioid in character. Thus our observations in the burned child were confirmed and extended by laboratory studies (Osgood et al., 1987).

We then tried exposure to cold as a less traumatic means of exploring the SIA of burns. A cold environment has often been used to study the endocrine effects of burn injury (Aprille et al., 1979), with the assumption that responses to cold and burn stress are the same. Although these experiments led to a long and interesting study of stress analgesia induced by cold in the rat, it was apparent early on that the hormonal response to cold was clearly different from that of burn injury (Osgood et al., 1990). \(\beta\)-endorphin plasma levels, for example, except for a minor initial increase, declined steadily throughout the 2 hours in the cold. Similarly, placing rats in a room held at a relatively high temperature (37°C) resulted in a \(\beta\)-endorphin response with a pattern very like that occurring during cold exposure (Figure 3). Thus neither of these procedures proved to be a suitable substitute for burn injury in these experiments.

The pharmacological properties of many drugs are altered by burns (Martyn, 1986). The magnitude and direction of such changes can be predicted by the rat model for burn injury (Bowdle et al., 1980; Fruncillo and DeGregorio, 1984). This paradigm has been of great value to us in characterizing the pharmacodynamic and pharmacokinetic attributes of analgesic agents in the burned subject. (These terms are often translated as "what the drug does to the body and what the body does to the drug," respectively). In one such study we found the predominately kappa opioid receptor antagonist butorphanol had greater po-

![The effects of a warm environment (37°C) on pain perception in the rat](image)

**FIGURE 3** In nonburned rats exposed to a warm (37°C, 99°F) environment there was a decline in tail-flick latency (closed circles) and a minor increase in plasma \(\beta\)-endorphin (open circles). These experiments were a part of an unsuccessful effort to find a substitute for burn injury in the rat.

![Graph showing the decrease in morphine plasma concentrations after a single intravenous dose](image)

**FIGURE 4** The decrease in morphine plasma concentrations after a single intravenous dose. The upper line (diamonds) show mean values from a group of 10 children with severe burns (greater than 80 percent of the body surface area); the lower line is from a group of 10 children with burns of less than 75 percent. The ordinate is percent change in morphine concentration (from time 0) and the abscissa time in minutes. The elimination of morphine was significantly more rapid in the group with smaller burns.
tency in the burned than the sham-burned rat (Osgood et al., 1988), while the disposition (pharmacokinetics) of this analgesic proved to be similar in both groups (Osgood et al., unpublished).

In current work we are examining the effects and disposition of morphine, probably the most commonly used analgesic in burn victims, in both the burned child (Figure 4) and rat (Osgood et al., in press; Osgood et al., 1986c). Overall there is close agreement in findings between the two groups, but in a homogeneous rat population, we are better able to define the influence of such things as burn size and time after injury on the pharmacology of morphine.

Studies in both the clinic and laboratory have contributed to improved pain management in the burned child, and further work may help to continue a steady advancement towards the amelioration of pain in these children.

REFERENCES


