Modern pain therapy widely follows the WHO (World Health Organization) guidelines using a three-step ‘ladder’ for pain relief. This escalating step scheme includes the administration in the order nonopioids, mild opioids and strong opioids, and adjuvants at any step. Analgesics should be given ‘by the clock’ rather than ‘on demand’. However, the chronobiological parameters circadian pain rhythm, circadian efficacy of analgesics, and individual circadian need for analgesics are to be considered. The results of a multitude of studies in chronobiology are not consistent. Therefore, further studies with standardized protocols are needed that allow to assign more consistent rhythms to diseases, pain causes, and analgesic efficacy of opioids. In many cases, each patient perceives pain and its intensity individually during the time of day. By administration of analgesics over a constant or continuous dosage time fluctuations in pain perception and the outcomes of many studies in chronobiology are ignored that prove the influence of biological rhythms on the pharmacokinetic and pharmacodynamic aspects of analgesics. As different types of pain show different rhythms (highest pain intensities arising at different times of the day) analgesics should be dosed flexibly. It is also very important that drug therapy can be adjusted individually to the pain rhythm of the patient as well as to the type and cause of pain. In severe pain therapy should be particularly careful. A flexible dosage depending on pain intensity and rapid dose adjustment are essentials of a modern pain therapy. Therefore, opioids that are flexible to use are better suited to treat the individual pain of the patient than rigid modified release oral or transdermal systems.

INTRODUCTION

Most of the physiological functions of all living things, including human beings, are subject to significant variations in circadian rhythm. Today, the existence of internal clocks that control circadian rhythms has been established down to the level of molecular biology. The principal clock is situated in the suprachiasmatic nucleus. Chronobiology is the study of recurrent biological rhythms that regulate the timing of life processes and thus usefully synchronize, in many areas, the interplay of different functions. The rhythmic phenomena of life include not only the universally familiar sleep/wake pattern as well as respiration and heart beat but also the blood pressure, smooth muscle tone, peristalsis, motor system, heart rate, organ functions, mental...
functions, and nerve activity (reviewed by Hildebrandt et al.²). Circadian rhythms can also be detected down to the level of hormones, receptors, and the consecutive signal transmission processes between and within the cells, enzyme kinetics, and gene regulation.

Chronopathology makes connections between diseases and disturbances in biological rhythm, such as the cardiac and respiratory rhythm, the sleep/wake pattern, the rhythm of the menstrual cycle, and disturbances in other rhythmic life processes. Disease leads to loss of synchronization, and even numerous diseases exhibit their own characteristic time structures. In humans, pathophysiological events such as myocardial infarction, angina, strokes, asthma attacks, allergic reactions, rheumatic symptoms, and gastrointestinal ulcers among others do not occur with equal frequency over 24 h but follow a pronounced circadian pattern.

Not only may the pharmacological effects of pharmaceutical agents follow circadian patterns, but also their pharmacokinetics can vary significantly depending on the time of day. Clinical studies have demonstrated that, for numerous drugs, circadian rhythms play a significant role in absorption, systemic distribution, and renal function. Circadian rhythms should, therefore, be taken into account when assessing the efficacy and therapeutic index of a drug.¹

CIRCADIAN RHYTHMS AND PAIN

Today, considerable information is available about circadian rhythms and their effects on the pharmacokinetics and pharmacodynamics of drugs, and hence of analgesics. As experience indicates that the treatment of both acute and chronic pain is frequently complex and also inadequate in many cases,⁵ better understanding of circadian pain behavior and the circadian effects of analgesics would appear to be important in order to be able to use the latter in accordance with circadian pain intensity. In addition, it should be borne in mind that perception of pain can vary substantially from one patient to another.⁴ In many cases, therefore, conservative therapy strategies, which can be individually adjusted to the patient's pain pattern, are beneficial.

CIRCADIAN VARIATIONS IN PAIN INTENSITY

The perception of pain is accompanied by higher level circadian processes, in which the circadian rhythms of endorphin and encephalin concentrations in the relevant pain-processing centers in the brain play a fundamental role.⁵ In recent years, a large number of studies have shown that the intensity of the perception of pain and reactions to painful stimuli are cyclical in nature and depend on the time of day (Table 1).

In a series of experiments in which the pin-prick pain threshold of the skin on the fingertip was determined, a circadian-related reduction in sensitivity was apparent at about 03.00 h and sensitivity to pain was at its height in the hours around mid-day. Circadian variations clearly have a plausible relationship with alertness.²

In another experiment, the circadian rhythm of the sensory pain threshold was determined in the teeth.⁵ The sensitivity of the teeth was at its nadir at the maximum pain threshold between 15:00 and 18:00 h, while the highest tooth pain intensity, together with the lowest pain threshold, occurred at about 08:00 h involving a 160% increase. The sensitivity threshold of the gums to a cold stimulus was at its maximum at 18:00 h and at its nadir at about 03:00 h.

Labor pain also follows a chronobiological pain cycle.⁶ Pain intensity was determined using a visual analogue scale (VAS 0–100; 0 = no pain, 100 = the worst pain imaginable). The 222 subjects surveyed stated that pain scores were higher at night than during the day. Scores were lower (72.9 ± 14.9) in the morning than in the afternoon (84.2 ± 15.9), evening (87.6 ± 14.6), and at night (83.5 ± 13.7).

These findings should be taken into consideration in clinical practice. More complex dental procedures could be scheduled for the afternoon or early evening; in the case of epidural analgesia in obstetrics, higher dosages of the local anaesthetic and opioid combination should normally be selected at night.

Fibromyalgia pain also shows a marked circadian rhythm. According to measurements using a VAS (0–100 mm), patients reported that the most severe pain occurred in the morning and the least severe in the afternoon.⁷ It is striking that pain thresholds do not follow the same pattern in all human tissues. Thus, skin sensitivity to heat radiation is at its minimum at 18:00 h and its maximum at 06:00 h. Pain intensity provoked by electrical stimulation, in contrast, is 70% higher at night than during the day.⁸

Chronic pain is also subject to a circadian rhythm, but no consistent pattern pertains here. In the case of rheumatoid arthritis, one study showed that the most severe pain was observed in the early morning.⁴
whereas the highest intensities of chronic carcinoma pain occurred in the evening in most patients affected. Circadian rhythms vary according to the type of pain. This means that divergent findings emerge from studies conducted in humans, in contrast to experimental animal studies. In many cases, the pattern of pain obviously depends on specific conditions, the diverse types of pain, and different diseases. As a result, therefore, every pain therapy regimen should be flexible, so that it can be adjusted to meet individual patient need. However, a flexible dosing regimen may mean that drugs must be taken more frequently and can thus lead to lower patient compliance. This is demonstrated by studies from the fields of antihypertensive or antidiabetic therapy. In these cases, discontinuing the medication has consequences that, at first, are not exactly serious. The situation in patients with severe and very severe pain would appear to be different: taking a potent analgesic at least twice daily gives these patients the certainty of reliable pain relief for about 12 h. As Nicholson et al. were able to demonstrate in their study, patients are even willing to take analgesics up to four times daily. Compliance is consequently not synonymous with individually efficient analgesia.

**DIURNAL VARIATIONS IN ANALGESIC EFFECT**

The effects of analgesics on sensitivity to pain are also subject to circadian variation. The relevant studies have been predominantly conducted in animals. As early as 1967, it was demonstrated using the hot plate test that morphine-induced analgesia undergoes circadian variations. The investigators observed that maximum analgesic effect was obtained in mice in the evening at about 21:00 h, during the activity period of these nocturnal animals, whereas the minimum analgesic effect occurred at about 15:00 h during the resting phase.

Another study demonstrated that analgesia with the same morphine doses has effects that differ in strength when administered to mice at two different times of day. The analgesic effects of morphine were substantially stronger at about 03:00 h, in the middle of the active phase, than in the middle of the animals' resting phase at 15:00 h.

In a more recent animal study from Japan, mice were also subjected to the hot plate test during a 12-hour light/dark cycle (light from 7:00 to 19:00 h). On days 1 and 2, a more pronounced analgesic effect occurred after daily morphine injections at about 21:00 h than after those administered at 09:00 h. In these nocturnal animals, the analgesic effect was significantly greater in the dark phase than in the light phase. According to Yoshida and colleagues, this effect is closely related to increased endorphin and encephalin concentrations and the 24-hour expression pattern of μ-opioid receptors. As early as 1981, it was reported after experiments with mice using the hot plate test that the rhythmic pattern of pain reaction is connected with the increase in endorphin and encephalin, the endogenous ligands for opioid receptors. Using an experimental design to determine μ-opioid receptor binding in the brain stem of mice, Yoshida and colleagues established that the number of these receptors was significantly higher at 21:00 h than at 09:00 h. The Japanese authors concluded that the 24-hour rhythm of endogenous opioid activity and μ-opioid receptor expression appears to be primarily responsible for the pattern of the basal perception of pain in rodents when no analgesic is administered.

Other authors also report a close relationship between pain and the rhythmicity of endorphin and encephalin concentrations in the plasma on the basis...
of animal studies. To date, little is known about circadian variations in endorphin and encephalin concentrations in humans. Today, however, it is agreed that specific opioid receptors are also present in the human brain and that, through synthesis of the oligopeptides endorphin and encephalin, specific endogenous ligands for these receptors also exist in the brain. The peak analgesic effect of morphine that occurs in rodents in their activity period (at night) can, according to Lemmer, also be observed in humans although in this case, translated into the corresponding active daytime period. A radioimmunological study supplied an initial indication of rhythmic variations in opioid receptor binding with peaks in the morning at 10:00 h and a nadir at 22:00 h. Petraglia et al. found peak values for \( \beta \)-endorphin at 8:00 h and trough values at 20:00 h in six healthy volunteers and reported similar results. It is difficult to derive a clear pain pattern from these connections, as many other influences cause variations in circadian rhythms.

**DIURNAL VARIATIONS IN OPIOID REQUIREMENT**

The variations in the intensity of severe pain can be derived from the opioid requirement of the patients affected. It not only varies diurnally but is also dependent on the type or cause of the pain (Table 2).

In the first chronopharmacological study with patient-controlled analgesia (PCA), patients were able to determine their morphine requirement themselves after gastric surgery. It emerged that, on postoperative days 1 and 2, a peak morphine requirement occurred at about 09:00 h, whereas the lowest requirement was observed at 03:00 h. The morning doses were on average 15% higher than those in the evening. Another working group reported results differing from those above. In a double-blind study, 55 patients, who had undergone surgery for gynecological carcinoma, where the patients self-administered either morphine sulphate or hydromorphone for pain relief using a pump at four-hourly intervals. The requirement for both opioids was significantly higher between 4:00 and 8:00 h and significantly lower for morphine between 12:00 and 16:00 h and for hydromorphone between midnight and 4:00 h. Morning doses were about 60% higher than doses administered at other times of day (Figure 1).

The same group reported on a study in which 45 gynecological cancer-patients were also given morphine postoperatively using patient-controlled medication. In these cases, the highest morphine doses were administered by the patients between 8:00 and 12:00 h and the lowest doses between midnight and 4:00 h.

In a further study, eight carcinoma patients were given a basal injection of hydromorphone, combined with PCA or with continuous infusion of the opioid. The pain intensities measured at 4-hour intervals using a VAS indicated that the pain was twice as severe at 22:00 h as it was at 14:00 h. Hydromorphone requirement peaked between 18.00 and 22:00 h and was at its lowest between 2:00 and 6:00 h.

The time at which an analgesic is administered also appears to impact on the duration of analgesia. This was observed in a study performed in 77 healthy women in the active phase of labour, when they received epidural fentanyl either during the day or

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cause of pain</th>
<th>Opioid</th>
<th>Time of max. requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves et al.</td>
<td>Stomach surgery</td>
<td>Morphine</td>
<td>9:00</td>
</tr>
<tr>
<td>Auvil-Novak et al.</td>
<td>Surgery for gynecological</td>
<td>(a) Morphine</td>
<td>(a) 0:00–4:00</td>
</tr>
<tr>
<td></td>
<td>carcinoma</td>
<td>(b) Hydromorphone</td>
<td>(b) 4:00–8:00</td>
</tr>
<tr>
<td>Auvil-Novak et al.</td>
<td>Gynecological carcinoma</td>
<td>Morphine</td>
<td>8:00–12:00</td>
</tr>
<tr>
<td>Vanier et al.</td>
<td>Carcinoma</td>
<td>Hydromorphone</td>
<td>18:00–22:00</td>
</tr>
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Table 2. Examples of variations in circadian opioid requirement

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Measurements of pain intensity on a VAS showed that analgesia persisted for longer (92 min on average) after daytime administration than after nocturnal administration of the analgesic (67 min on average). The 27% difference in the duration of analgesia was thus clear. However, other influencing factors, such as anxiety for example, might also have played a part.

A marked circadian rhythm in pain intensity is also evident during treatment with long-acting opioids. This was observed in a study with 42 carcinoma patients, who were treated either with oral doses of sustained-release morphine or buprenorphine. Maximum analgesic effectiveness was shown to occur at 22:00 h in the evening or at 02:00 h in the morning, whereas the least impact on pain intensity was observed in the morning at 10:00 h. The same group measured pain intensity in 20 carcinoma patients using a verbal rating scale (VRS). The patients were given 16 mg (nonsustained-release) morphine at 4-hour intervals round the clock. Afterwards, the highest pain intensities were measured between 8.00 and 22:00 h during the day, while at night they were lower.

**NATURE OF OPIOID ADMINISTRATION**

The use of opioids for the management of pain generally follows the WHO guidelines. Despite much criticism it can be considered a proven didactical tool for the implementation of pain therapy itself. The prompt oral administration of drugs in the order: nonopioids such as NSAIDs or dipyrone, mild opioids such as tramadol or codeine, and then strong opioids such as morphine, is widely known as the ‘WHO step scheme.’ For the management of side-effects additional drugs are often necessary. To maintain freedom from pain, drugs should be given ‘by the clock,’ rather than ‘on demand.’ This procedure is regarded effective in 80–90% of cases.

In the recent years, sustained-release and ultra-sustained-release opioid formulations are significant new developments. Despite all their advantages, such as pain therapy in terms of pain prophylaxis, a very long rate of absorption and thus lower risk of addiction, none of which should be dismissed, the best sustained-release formulation does not exempt the physician from the duty to take the individual ‘pain pattern’ of a given patient into account in the treatment plan in question. Experience has shown that different pain entities also require correspondingly variable approaches. So, if a cancer patient, for example, has the highest analgesic requirement between 10:00 and 18:00 h, and a patient with rheumatoid arthritis, in contrast, in the early hours of morning, this should be borne in mind in therapy. For individual therapy with opioids, this means in practice that oral sustained-release preparations with effects lasting for 12 h can be administered at different doses in the morning or evening as required. As clinical practice shows, when oral ultra-sustained-release formulations or transdermal systems are used, supplementation with short-acting opioid...
formulations with a rapid rate of absorption is frequently needed, because of break-through pain.

Different studies have compared the efficacy of a long-acting controlled release formulation administered once daily with shorter-acting formulations of morphine administered twice daily. In a double-blind crossover study, patients with chronic stable pain were given total daily doses of 20–120 mg. The long-acting once-daily administration proved to be equally effective and was as well tolerated as the twice-daily administration. Similar results were obtained by Rauck et al. when treating patients with moderate to severe chronic lower back pain, by Bruera et al. in patients with chronic carcinoma pain and by Nicholson et al. in patients with moderate to severe chronic nonmalignant pain. Understandably, the patients found once-daily administration to be more pleasant and convenient. The quality of sleep improved significantly with both formulations but much more markedly on therapy with the long-acting once-daily administration. A long-acting formulation, therefore, can be used without complications in patients with chronic stable pain. However, it is important to bear in mind that, in these studies, pain was not measured over the course of the day and thus variations in pain intensity were not recorded. Furthermore, it is possible that, with twice-daily administration, the potential for flexible dosing of these analgesics was not fully exploited. The question remains of what results would have been achieved with asymmetrical dosages. To date, no clinical studies are available on this issue.

Initial indications of the benefit of flexible dosing, adjusted to the pain, are supplied by data from an observational study of tumor patients and multimorbid patients. Their perception of pain is often subject to substantial diurnal variations, which means that their requirement for analgesia varies accordingly. In these cases, asymmetrical twice-daily opioid administration led, despite the varying pain level, to substantial improvement in the situation. This was evident in the study in question performed in 1286 patients with severe and very severe pain, in which sustained-release hydromorphone, adapted to the pain, was administered at a higher dose in the morning and lower dose at night, leading to consistently low pain intensities.

Transdermal systems are fundamentally useful in patients with dysphagia who have stable pain levels and an average opioid requirement. According to EAPC guidelines, transdermal systems are effective alternatives to oral opioids and thus an enrichment of the therapy spectrum, but should always be reserved for those patients who meet the above conditions.

Transdermal opioid administration can also result in substantially more rescue medication being necessary. This was established in the context of a study in which 202 patients with carcinoma pain were treated either with a fixed administration system (transdermal fentanyl) or flexibly every 12 h with sustained-release oral morphine. In 53.9% of cases under the fixed system and 41.5% on flexible administration, rescue medication had to be given. There is no evidence for the belief that transdermal administration generally leads to less frequent constipation and daytime sleepiness, or more frequent insomnia and a shorter duration of sleep.

It must be borne in mind that palliative-care patients are often treated in the high dose range. Patch therapy is often problematic because of the associations described above and not least because substantial variations in pain intensity are frequent. The positive aspects should not be underestimated: individualized administration of medication by the nursing staff means additional social contact for the patient. It is known that changes in metabolism are present in palliative-care patients in the terminal phase, which make s.c. or i.v. administration of opioid medication necessary. It is inappropriate, however, to discuss these problems in more detail here.

**CONCLUSIONS**

1. Pain is subject to significant circadian variation.
2. Depending on the cause and nature of the pain, there is a marked circadian rhythm in pain intensity.
3. The effects of pharmaceutical agents and their pharmacokinetics are subject to significant diurnal variations.
4. Rigid dosage regimens, such as transdermal systems and oral, ultra-sustained-release once-daily dosages have benefits in chronic stable pain but, in the case of strong variations in pain intensity, e.g., in tumor pain, they often do not meet the individual patient’s actual requirement.
5. Asymmetrical twice-daily opioid administration can bring about a substantial improvement in fluctuating pain levels and offer the patient more security.
REFERENCES

8 Junker and Wirz: Chronobiology: influence of circadian rhythms on the therapy of severe pain


