Lesson of the week

Morphine induced allodynia in a child with brain tumour

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Morphine is the drug of choice for patients with severe acute or chronic pain, especially those with intractable pain associated with malignant diseases. The drug is metabolised by the liver into morphine-3-glucuronide and morphine-6-glucuronide. The glucuronides are mainly eliminated via bile and urine.¹ Morphine-6-glucuronide binds to opiate receptors and can be detected in the cerebral fluid after systemic administration; its analgesic effect is 40 times as potent as that of morphine itself.² In contrast, morphine-3-glucuronide, which represents the major plasma and urinary metabolite of morphine, antagonises the effect of morphine and morphine-6-glucuronide.³

According to the World Health Organisation's recommendations for treatment of cancer pain, the morphine dose should be adapted to the individual patient. Therefore, if patients complain of an insufficient analgesic response to standard morphine dosage, they should receive higher doses, which may exceed hundreds of milligrams of morphine hourly.⁴ In a few adults treated with higher dosages for prolonged periods of time, morphine induced hyperalgesia or allodynia develops.^{5, 6}

Allodynia has been provoked in Sprague-Dawley rats. These animals are unable to metabolise morphine to morphine-6-glucuronide, and thus morphine-3-glucuronide is the major morphine metabolite. A noticeable inverse relation was observed between the mean degree of analgesia and ratio of plasma morphine-3-glucuronide to morphine.⁷ Consequently, a raised morphine-3-glucuronide to morphine-6-glucuronide ratio seems to be responsible for the phenomenon of hyperalgesia and allodynia.

There are only a few reports analysing the ratio of morphine and its metabolites in adult patients and children of various ages.⁸⁻¹⁰ Children metabolise morphine differently from adults, and the morphine-3-glucuronide to morphine ratio, in particular, is dependent on age. In addition, the plasma morphine-3-glucuronide to morphine-6-glucuronide ratio in children is half the ratio in adults.⁶⁻⁸

Allodynia and hyperalgesia induced by high amounts of morphine have already been described in adult patients.¹¹ However, to our knowledge, morphine induced hyperalgesia has not been reported in children so far.⁵ In addition, in many previous articles concerning adult patients with hyperalgesia, the morphine and metabolite plasma concentrations were not measured.¹²

Case report

A 9 month old girl presented with astrocytoma of the hypothalamus that had been incompletely resected and remained inoperable because of its position. Progressive tumour growth resulted in impaired speech, gross motor functions, and swallowing at the age of 21 months. Parenteral nutrition became necessary because of persistent vomiting. When routine nursing resulted in pain, treatment with tramadol was started, and a

Schedule of morphine dosage and additional drugs. Plasma concentrations of morphine and its metabolites were measured on days 60, 69, 81, and 99

continuous infusion of morphine in a dose of 10 g/kg per hour was instigated when tramadol proved ineffective. When sporadic seizures further complicated the course of the disease on day 16 and day 20, phenobarbital (10-15 mg/kg per 8 hours; day 16) and then flunitrazepam (0.04 mg/kg per hour; day 47) were added, but no impact on pain relief was achieved. A stepwise increase in the morphine dose resulted in sufficient pain relief for periods of only a few days during the next three weeks. Even when the dose was further augmented up to a maximum of 6950 g/kg per hour (2.5 g per day) during the following 4 weeks, the child showed extreme discomfort, cried, and moaned during routine care procedures such as nappy changing, feeding, or washing. In this situation morphine induced hyperalgesia and allodynia was suspected, and the morphine dose was reduced (day 53). At irregular intervals over the next month the dose was reduced by 50% until a dose of 280 g/kg per hour was reached (day 78). When morphine was reduced the following drugs were given: methotrimeprazine (levomepromazine; 0.1 mg/kg per 8 hours) to improve sedation, dexamethasone (1 mg/kg per 6 hours) to reduce intracranial pressure, and dipyron (20 mg/kg per 8 hours) as a peripheral analgesic agent (figure).

Within 1 week the symptoms of allodynia had resolved and the child was able to tolerate care procedures well. Concentrations of plasma morphine, morphine-3-glucuronide, and morphine-6-glucuronide were determined on four different occasions (days 60, 69, 81, and 99) and were high, particularly the ratio of morphine-3-glucuronide to morphine (table). When the morphine dose was further reduced, the ratios also fell, but after some delay, possibly because of renal

Hyperalgesia and allodynia induced by morphine can complicate treatment for pain in terminal care

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insufficiency.¹³ Until her death at the age of 28 months, the patient was almost free of pain and sufficiently sedated.

Discussion

Morphine induced hyperalgesia, allodynia, and myoclonia have been described in adult patients.⁵⁻¹¹ Hyperalgesia is defined as an increased response to a stimulus which is normally painful, and allodynia is defined as pain caused by a stimulus which does not normally provoke pain. These phenomena were observed after large amounts as well as after small doses of morphine. In view of the young age of our patient we can only speculate that she suffered more from allodynia than hyperalgesia since even routine nursing procedures seemed to cause pain.

The observation that hyperalgesia can be caused by morphine itself or by its metabolites is so far supported only by data from animal studies. Smith et al showed in experiments with Sprague-Dawley rats that morphine-6-glucuronide given intracerebroventricularly had a good analgesic effect.³ The administration of morphine-3-glucuronide alone produced allodynia, hyperalgesia, and tremor in rats. In addition, these authors showed that morphine-3-glucuronide is a potent antagonist of the analgesic effect of morphine or, more specifically, morphine-6-glucuronide.³ Further experiments showed that high doses of morphine have a lesser analgesic effect than low doses. After high doses of morphine, the morphine-3-glucuronide to morphine plasma ratio was higher than after low doses. Thus, a high morphine-3-glucuronide to morphine ratio could be the explanation for this phenomenon. However, other studies focusing on neoplastic neuronal changes show that receptor mediated cellular and intracellular signal cascades, such as those observed after nerve injury and inflammation, might also contribute to morphine induced hyperalgesia.¹⁴⁻¹⁵

To our knowledge, the case presented here is the first to show that children are also prone to morphine induced hyperalgesia and allodynia. There are only a few reports detailing plasma concentrations of morphine and its metabolites in children. Choonara et al found a mean plasma morphine-3-glucuronide to morphine ratio of 23.9 (SD 6.4) in children aged between 1 year and 16 years.⁹ The plasma ratio was threefold to fivefold lower in premature neonates and infants than in older children.¹⁰

When morphine induced allodynia was suspected in our patient, the absolute morphine plasma concentration was not extremely high, although large doses had been given. However, the morphine-3-glucuronide to morphine ratio was very high at 42 (table). The ratios approached normal values 3 weeks after the

dose of morphine has been reduced. Since the absolute plasma concentration of morphine did not correlate with the administered dose during the course of the treatment it might be more useful for ruling out allodynia to determine the metabolite ratios.

The WHO recommendation for treating tumour pain advises that the dose of morphine should be raised until the patient is free of pain.⁴ This works in most patients, but the possibility of morphine induced hyperalgesia or allodynia must not be overlooked.¹⁶ The morphine metabolite morphine-3-glucuronide may play an important part in the development of these phenomena. In contrast to adults, children exhibit an age dependent difference in drug metabolism and kinetics. The case presented here suggests that experimental results from animals on morphine induced hyperalgesia and allodynia also hold true for man. It also emphasises the importance of considering morphine induced hyperalgesia and allodynia in children who receive high doses of morphine without achieving sufficient pain relief.

In most clinical laboratories quantitative measurements of morphine and its metabolites are not performed routinely. The method of high performance liquid chromatography we used provides a specific, sensitive, and rapid assay. It is useful for the simultaneous determination of morphine and its metabolites in plasma and can rule out raised concentrations of morphine-3-glucuronide.

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MS initiated and coordinated the paper and acts as guarantor. The paper was written jointly by SH, CM, and MS; they discussed the core ideas and interpreted the findings. KO undertook the morphine analysis. UH collected blood samples, participated in the data analysis, and together with SH and CM looked after the patient.

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Plasma concentrations and ratios of morphine and its metabolites in relation to dosage

Day of treatment with morphine	Dose (µg/kg/h)	Plasma concentration (ng/ml)			Metabolite ratios		
		Morphine	M6G	M3G	M3G:M	M6G:M	M3G:M6G
52	6950	—	—	—	—	—	—
60	2200	72	330	2998	42	4.6	9
69	560	112	368	4139	36	3.3	11
81	280	80	148	1058	13	1.8	7
99	420	125	244	1778	14	1.8	7

M=morphine; M6G=morphine-6-glucuronide; M3G=morphine-3-glucuronide.

What is allodynia?

Allodynia is the term used when any normally painless stimulus is experienced as painful. Hyperalgesia is the experience of unusually heightened pain from a known painful stimulus. These two symptoms (together with myoclonus, seizures, agitation, and delirium) are well documented but rare side effects of opioids, particularly if renal function is poor (*Current Opinion in Anaesthesiology* 1998;11:436-45). Allodynia and hyperalgesia are thought to represent a hyperexcitable state, possibly induced via an antiglycinergic mechanism. The symptoms generally resolve rapidly when the dose of the opioid is reduced or another opioid is substituted, or both.

Both allodynia and hyperalgesia should be considered if a patient is already using high doses of the opioid or if the beginnings of hyperexcitability are observed. Better control of symptoms may be achieved by using combinations of analgesics with different mechanisms of action or neural blockade techniques rather than simply increasing the dose of the opioid in patients whose pain is uncontrolled.

Allodynia and hyperalgesia have been observed with several opioids, including morphine. In the

case of morphine, there is little direct evidence that these effects are due to either the accumulation of morphine or its metabolites. They may be caused by both (*Pain* 1998;74:43-53), or by particular morphine to metabolite ratios. It is suggested, however, that two common metabolites—morphine-3-glucuronide and morphine-6-glucuronide are implicated. Animal studies have shown that high concentrations of morphine-3-glucuronide can antagonise morphine, thus reducing the analgesic effect of morphine (*Pain* 1995;62(5):1-60; *Journal of Pharmaceutical Sciences* 1998;87:813-20); and to some extent this may be happening in humans. Under normal circumstances, however, morphine is effective, despite the fact that up to 75% of it is metabolised to morphine-3-glucuronide in humans and the concentrations of morphine-3-glucuronide greatly exceed those of morphine. It is not always appropriate to extrapolate what happens in animals to humans. The metabolism of morphine, and indeed the receptor population via which the parent drug (or its metabolites) are acting, may be quite different in the two species.

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Science
commentary

Diversity to divinity

In the fortnight in which nail bombs tore through ethnic minority neighbourhoods in Brixton and Brick Lane and brought mayhem to Soho, a little known, relatively unpublicised event took place in the Midlands that should give hope to all who wish for harmony between Britain's communities.

This event was the consecration of a new Hindu temple on 13 acres of derelict land set in the bleak industrial landscape of Tividale in Sandwell.

Sitting out in the unexpected sunshine of a May bank holiday weekend we contemplated a scene that represented everything that a tolerant multicultural society stood for and that defied the perversely logical potential of nail bombs to spread fear and discord. The need for tight security—after all, a government minister was among the invited dignitaries—did not dampen the obvious enthusiasm of the more than 5000 people who took part in the festivities. Amid a deeply moving display of religious devotion and a dazzling exposition of south Asian culture, a new Hindu temple was established in Britain.

Speaking at the same time in nearby Birmingham on the occasion of the 300th anniversary of the founding of the Sikh Khalsa, the prime minister, Tony Blair, spoke of a "modern civic society" in which discrimination and violence have no place. As public health physicians we recognise that this vision represents one of the prerequisites for health so eloquently espoused by Health for All 2000.

We were among thousands of people who converged from all over Britain to join together in consecrating the new Hindu temple. Remarkably, many of those present were not of the Hindu faith, the host community being represented in fair numbers and at the highest level. Recognising the multicultural nature of the development, the millennium commission part funded the project. It was as much a celebration of art and culture as of religion, and in this too there was participation by all communities.

There are spin-off benefits from the temple. The multipurpose hall will soon be turned into a healthy living centre. The Sacred

Lands project is a unique effort at transforming the derelict land on which the temple was built into a landscaped haven of peace and beauty for the local community to enjoy and cherish. Tourist money will be attracted to an area not previously on any tourist map.

Interestingly, the project is the brainchild of a group of Indian doctors working in the NHS. For many it was an emotional moment to see their efforts of many years take shape. Overseas doctors, it is often said, are the unsung heroes of the NHS, their contribution understated and undervalued. But here in Tividale their commitment to the temple project and to Britain was amply recognised and richly rewarded.

We believe the new temple is a successful symbol of the diversity of the British way of life. The prime minister believes that a civilised society should respect this diversity. Diversity might occasionally lead to discord, but as long as we value our differences and respect each other's religion there will be hope for an equal and civil society.

The Sri Venkateswara Temple in Sandwell is a powerful symbol of the inherent good in British society where diversity leads to divinity.

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We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.