

CASE REPORTS

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Insidious Intoxication After Morphine Treatment in Renal Failure: Delayed Onset of Morphine-6-glucuronide Action

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MORPHINE-6- β -GLUCURONIDE is a metabolite of morphine with potent opioid agonist activity.¹ It is eliminated by the kidney, and therefore, accumulates in patients suffering from renal failure potentially causing long lasting opioid effects.² Morphine-6-glucuronide crosses the blood-brain barrier much slower and to a much smaller extent than morphine.³ The slow transfer of morphine-6-glucuronide from the blood into the brain probably prevents building up brain levels sufficiently high to cause intoxication in patients with normal renal function. It also prevents morphine-6-glucuronide from exerting central nervous opioid action after its short-term administration.⁴ However, we describe a case that illustrates the clinical significance of the slow transit of morphine-6-glucuronide to and from the effect site (brain) in a patient suffering from renal failure.

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The presented plasma concentrations of morphine and its metabolites and a brief mentioning of presented case were part of a previous publication concerning employed assay: Bourquin D, Lehmann T, Hammig R, Bühler M, Brenneisen R: High-performance liquid chromatographic monitoring of intravenously administered diacetylmorphine and morphine and their metabolites in human plasma. *J Chromatogr B* 1997; 694:233-8.

Key words: Analgesia; pharmacokinetics; metabolism.

Case Report

A 22-yr-old man with Goodpasture syndrome resulting in end-stage renal disease and severe arterial hypertension underwent bilateral nephrectomy. He received 40 and 30 mg of morphine, respectively, as the sole analgesic at the beginning and at the end of the 3.5 h surgery (intravenous bolus injections). Postoperative patient-controlled analgesia using morphine was installed. The patient indicated mild pain at rest and severe pain when moving and self-administered 36 mg of intravenous morphine during the first 18 h after surgery and another 36 mg during the following 13 h. His morphine demand during the first 18 h after surgery was higher than approved by the patient-controlled analgesia setting. The patient became unconscious 31 h after surgery and remained in that state for 45 h. This time course was also reflected by the results of vigilance tests administered in the postoperative period (Galveston orientation and amnesia test,⁵ digital span test assessing how many ciphers can be repeated correctly, and reaction time to a visual stimulus). Despite profound unconsciousness respiratory depression was clinically not prominent. As part of a routine managing unconscious patients, 2-4 l · min⁻¹ of oxygen by nasal probe was administered. The hemoglobin oxygen saturation remained above 93% except for one occasion 66 h after the end of surgery (resolved after suctioning of intratracheal secretion). The patient underwent hemodialysis 45 h, 88 h, and 162 h after surgery. He was unconscious during the first hemodialysis and remained in that state 34 h thereafter.

Blood samples were drawn in the pre- and postoperative period to assay for plasma concentrations of morphine and its glucuronide metabolites using high performance liquid chromatography.⁶ When the patient became unconscious 31 h after surgery, the morphine plasma concentration had been below the lower limit of quantification of 2 ng/ml for more than 26 h.⁶ On the other hand, morphine-6-glucuronide concentrations had already been close to their maximum for 26 h. The hemodialysis starting 45 h after surgery almost completely cleared morphine-6-glucuronide from plasma. However, the patient did not regain consciousness until 34 h after hemodialysis (see fig. 1).

The equilibration half-life of morphine-6-glucuronide between plasma and the brain was estimated using a nonparametric approach. It was consistently long with 36 h, 58 h, or 161 h when the Galveston orientation and amnesia test, reaction time, or digital span test data were used for the calculation, respectively.

Discussion

The present observation shows that in the setting of renal insufficiency severe opioid side effects can occur many hours after morphine plasma concentrations have peaked and morphine-6-glucuronide concentrations

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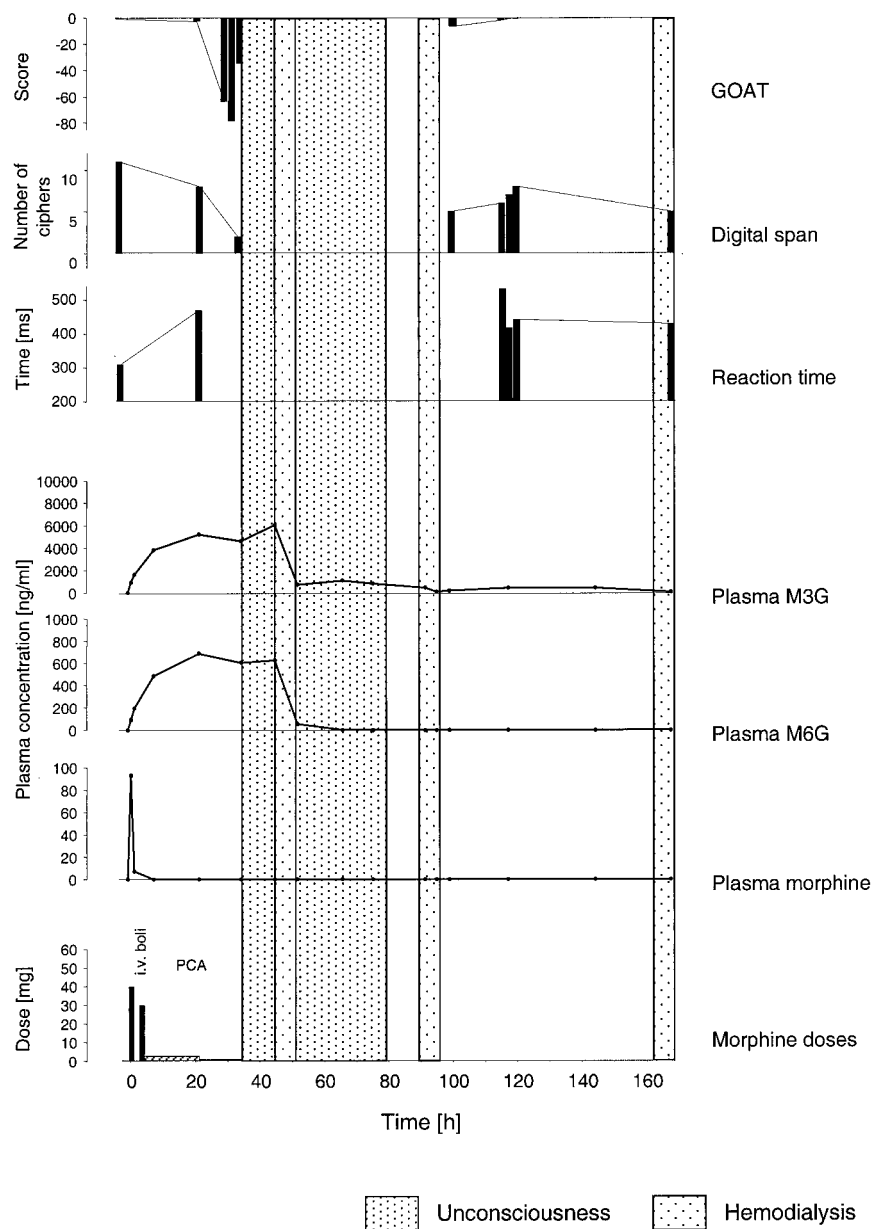


Fig. 1. For bilateral nephrectomy a total amount of 110 mg of intravenous morphine had been administered to a young man with chronic severe renal failure. Unconsciousness started at a time when morphine was no longer detectable in plasma, and morphine-6-glucuronide (M6G) concentrations had been high for more than a day. Hemodialysis starting 45 h after surgery almost completely cleared morphine-6-glucuronide from plasma. However, the patient remained unconscious for another 34 h. The slow equilibration of M6G between plasma and the brain seems to explain the long delay between reaching high plasma concentrations of M6G and the onset of unconsciousness, as well as the slow recovery from unconsciousness after clearing most M6G from plasma with hemodialysis. The time course of morphine dosage, the plasma concentrations of morphine, morphine-6-glucuronide, and morphine-3-glucuronide, and of the three parameters assessing the patient's vigilance (Galveston orientation and amnesia test [GOAT], digital span test, and reaction time to visual stimuli) are displayed.

have reached a plateau in plasma. These side effects are most likely mediated by morphine-6-glucuronide and not by morphine or morphine-3-glucuronide. The main morphine metabolite morphine-3-glucuronide does not exert depressant effects in the central nervous system.⁸ Morphine itself equilibrates too quickly from blood into the brain to account for observed delay of many hours between the plasma concentration *versus* time profile and the effect *versus* time profile, respectively. Despite two large intravenous doses of morphine during surgery the

patient experienced postoperative pain and continued to self-administer morphine by patient-controlled analgesia. At this time the high plasma concentrations of morphine-6-glucuronide did not seem to result in clinically relevant analgesia. However, with a delay of many hours similar plasma concentrations of morphine-6-glucuronide resulted in toxic side effects, *i.e.*, the patient became unconscious. As the slow transfer between plasma and effect compartment is the reason for the delayed appearance of opioid side effects, it is also likely to be

the reason why the patient remained unconscious for a long period after morphine-6-glucuronide had disappeared from plasma. Despite its elimination from plasma, it was probably still present at the effect site at high enough concentrations to maintain clinical opioid effects. Morphine effects probably having ceased before morphine-6-glucuronide effects becoming clinically relevant seems to explain why the patient continued to self-administer morphine by patient-controlled analgesia.

Despite profound unconsciousness the patient suffered little from respiratory depression. This is compatible with reports suggesting that morphine-6-glucuronide causes less respiratory depression than morphine.⁹ However, other investigators attributed profound respiratory depression to morphine-6-glucuronide rather than to morphine.^{2,10,11} Despite inconsistent reports on the relative potency of morphine and morphine-6-glucuronide in regard to respiratory depression, it is widely accepted that morphine and morphine-6-glucuronide exert differential pharmacodynamic activity at the receptor level. Both act mainly by stimulating μ -opioid receptor as recently confirmed by their drastically attenuated activity in μ -opioid-receptor knockout mice.¹² Morphine and morphine-6-glucuronide bind to the μ -opioid receptor with comparable affinity.¹ This contrasts with an up to 650-fold higher analgesic potency of morphine-6-glucuronide relative to morphine.¹ This discrepancy between functional and binding activity led to the hypothesis that morphine and morphine-6-glucuronide have differential binding affinity to variants of the μ -opioid receptor.

A single μ -receptor gene, MOR-1, has been identified.¹³ However, antisense mapping studies revealed that the *MOR-1* gene contains at least nine exons, and six distinct *MOR-1* receptors have so far been described.¹⁴ Interestingly, different exons of the *MOR-1* gene seem to code receptor variants involved in either morphine or morphine-6-glucuronide antinociception.¹⁵ When transcription of exon 1 of the MOR-1 receptor gene was inhibited by a specific antisense oligodeoxynucleotide, morphine antinociception in rats was blocked but morphine-6-glucuronide antinociception remained unchanged.^{15,16} In contrast, targeting exons 2 and 3 with antisense oligodeoxynucleotides decreased morphine-6-glucuronide but not morphine antinociception.^{15,16} The importance of exon 2 but not exon 1 for morphine-6-glucuronide mediated antinociception was also demonstrated in knockout mice.¹⁷ These results have led to the proposal that a distinct morphine-6-glucuronide receptor exists as a splice variant of the *MOR-1* gene.¹⁵ The

fact that different splicing variants of the *MOR-1* gene seem to mediate either morphine or morphine-6-glucuronide antinociceptive effect raises the question whether this is also true for other than antinociceptive effects. So far, there is evidence that exon 4, but not exons 1 to 3 are involved in coding the receptor mediating inhibitory effects on gastrointestinal transit. There is currently no information about the contribution of different *MOR-1* splice variants for mediating respiratory depression. However, in light of outlined findings one may speculate that the patient reported here has suffered from profound unconsciousness but not significant respiratory depression because of differential activity of morphine and morphine-6-glucuronide on receptor constituting different splice variants of the MOR-1 gene.

Monitoring of morphine plasma concentrations in the present clinical case would not have given any indication for upcoming severe opioid side effects. Even monitoring of morphine-6-glucuronide plasma concentrations would not necessarily have led to the conclusion of toxicity because morphine-6-glucuronide levels were high for a long time without clinical effects. Multiple dosing of morphine in patients prone to accumulate morphine-6-glucuronide is problematic and bears the risk of delayed severe intoxication since the effects of morphine-6-glucuronide will not become apparent for many hours. Replacement of morphine by opioids with pharmacokinetics that do not depend on renal elimination seems wise and drugs like tilidine, buprenorphine or sufentanil, should be considered.

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Dilated Nonreactive Pupils Secondary to Neuromuscular Blockade

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THE nondepolarizing neuromuscular blocking (NMB) agents do not readily cross the intact blood-brain barrier (BBB).^{1,2} However, when introduced into the central nervous system (CNS), NMB drugs and some metabolites

are known to be pharmacologically active. Cholinergic depression, autonomic dysfunction, neuronal excitotoxicity, seizures, and neuronal death have been reported.³⁻⁶ With the exception of the atracurium metabolite laudanosine, evidence suggests that these effects are mediated by neuronal nicotinic acetylcholine receptors within the CNS.⁴

In the critically ill patient population, disruption of the BBB may be present.⁷⁻¹⁰ In addition, prolonged high concentrations of NMB drug may accompany continuous administration. The combination of BBB disruption and high drug concentrations may produce central effects by these agents.

Short-term administration of NMB agents has been shown to have no effect on pupil size in healthy anesthetized patients.¹¹ We report three cases in which dilated, nonreactive pupils were time- and dose-dependently associated with the prolonged use of atracurium or vecuronium and return of pupil reactivity was temporally associated with discontinuation of the respective NMB agent. These pupil changes were not associated with administration or discontinuation of any other pharmacological agent.

These cases represent 12.5% (3/24) of all patients ad-

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Key words: Atracurium; mydriasis; neuromuscular blocking agents; pupillary light reflex; vecuronium bromide.