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Clinical pharmacology of morphine and morphine-6-glucuronide A PK/PD modeling approach

Jörn Lötsch*

Pharmazentrum frankfurt, Department of Clinical Pharmacology, Johann Wolfgang Goethe-University, Theodor Stern Kai 7, D-60590 Frankfurt, Germany

Abstract

The clinical pharmacology of morphine is complicated by its active metabolite, morphine-6-β-glucuronide (M6G). M6G is a potent μ-opioid agonist that has been recognized to play an important role in the clinical effects of morphine. However, M6G probably crosses the blood brain barrier with difficulties, and is of importance for the effects of morphine only during long-term morphine administration because only then M6G may reach high enough CNS concentrations. Since M6G is eliminated from the body via the kidney, it may cause severe opioid side effects with insidious onset and long persistence when renal function is impaired. This time dependent participation of M6G at the clinical effects of morphine makes it difficult to predict the effect of morphine in an individual patient. The problem may be solved using a PK/PD modeling approach to the clinical pharmacology of morphine that takes the delayed action of M6G into consideration.

Keywords M6G; Opioid; Metabolite

1. Pharmacological effects of morphine and M6G from a PK/PD modeling perspective

Morphine is metabolized to morphine-6-β-glucuronide (M6G) to approximately 10%. M6G is a potent opioid agonist that participates at the clinical effects of morphine. Fig. 1

* Tel.: +49-69-6860-4589; fax: +49-69-6860-7617.
E-mail address: j.loetsch@em.uni-frankfurt.de (J. Lötsch).

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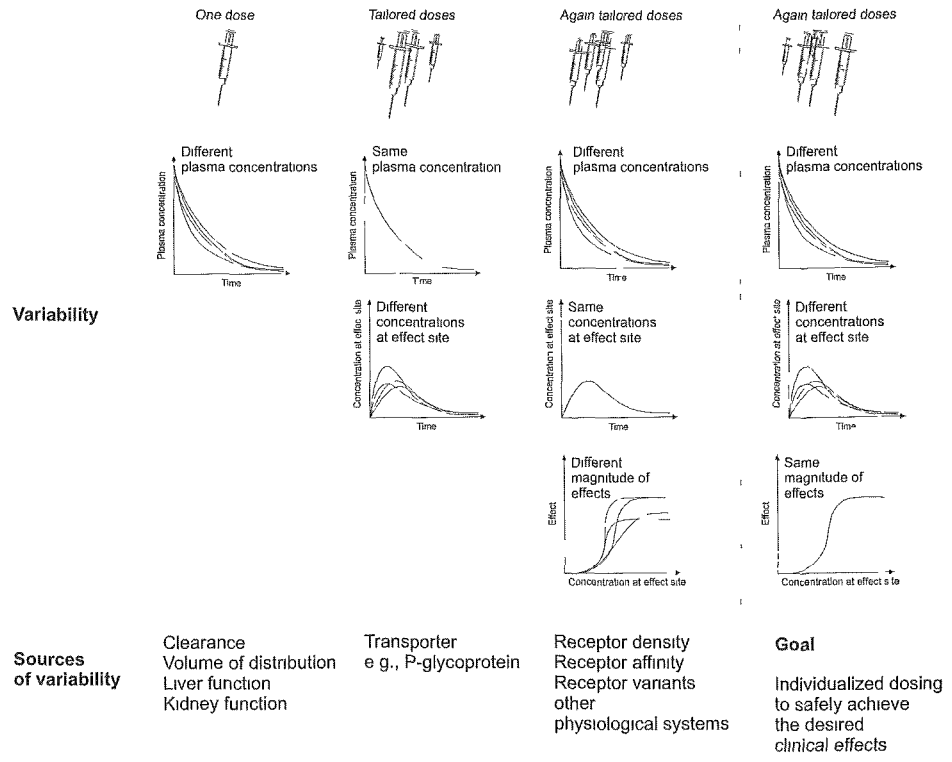

Fig. 1. Factors to be considered when attempting to individualize morphine dosing in order to achieve optimum treatment for a specific patient.

outlines the main sources of variability observed along the processes from morphine administration to opioid effect.

After administration of a certain dose of morphine, plasma concentrations of morphine and M6G vary among individuals depending on pharmacokinetic parameters such as clearance and volume of distribution. The clearance of morphine mainly depends on the subject's liver function and is impaired in liver cirrhosis [1]. In contrast, the clearance of M6G depends on the function of the patient's kidney. Severe M6G-mediated side effects had been reported after morphine administration in patients with renal dysfunction [2]. This was probably a result of the accumulation of M6G in plasma, which in turn led to an accumulation of the opioid at the site of effect, the CNS.

From plasma, morphine and M6G have to reach the effect site in order to exert their clinical action. When adapting the doing regimen that the same plasma concentrations of morphine and M6G are achieved in all patients, the concentrations at effect site may still vary among individuals. This variation may depend on parameters related to the transfer from plasma to effect site. While the value of the k_{e0} half-life for morphine appears to not

longer than a few hours [3,4], the effect of M6G builds up much slower, with a k_{e0} half-life of several hours [2,4]. Recent research employing measurement of pupil diameters for 16 h, after M6G administration, will allow for calculation of the value of M6G k_{e0} (unpublished results). Because of this long delay between the time course of the plasma concentrations and the time course of the effects, M6G appears to contribute little to the morphine effects during short-term morphine administration [5,6]. In contrast, it causes clinically relevant opioid effects during long-term morphine administration [7], when the time to build-up the effects had been long enough. This appears to be especially important for patients with renal failure in whom the M6G clearance is significantly decreased from about 150–11 ml/min [8].

The long delay between the time course of M6G plasma concentrations and the time course of its effects may be caused by a slow transfer of M6G between plasma and effect

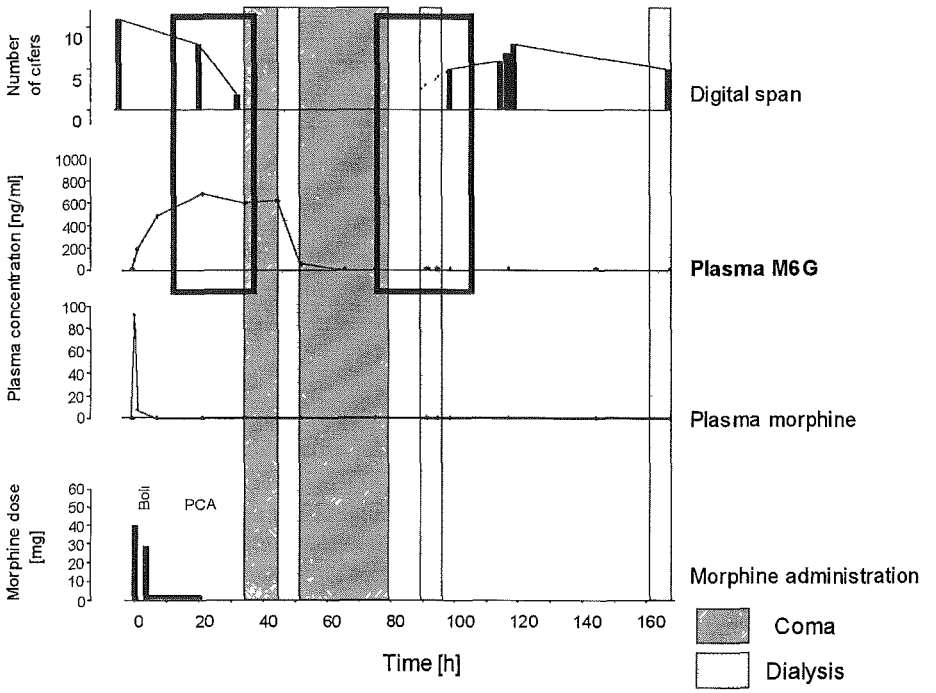

Fig. 2. A case of insidious opioid intoxication after morphine administration to a patient with renal failure who underwent nephrectomy. He received two intravenous bolus injections during surgery and was under morphine PCA after surgery. While morphine disappeared from plasma at 12 h after surgery, M6G accumulated in plasma, remaining at high levels until it was cleared from plasma by hemodialysis. Despite high plasma M6G concentrations having been present for many hours, the patient went unconscious only at about 24 h after morphine therapy was started. At that time, morphine had not been detectable in plasma for more than 12 h. On the other hand, it took another 24 h after M6G was cleared from plasma until the patient regained consciousness. This delay from the plasma concentration versus time course in both onset and offset of the effects was also seen in the digital span test (rectangles) [2].

site. The aforementioned case of M6G intoxication after morphine administration to a patient with renal failure [2] supports this hypothesis. That is, the delay between plasma M6G and opioid effects (coma, digital span, i.e. a test is that the patient was asked to repeat as much as possible out of 10 ciphers read to him) was seen in both onset and offset of the effects (Fig. 2).

A possible cause for inter-individual variability in the k_{e0} and, thus, in the time course of effect site concentrations of morphine and M6G are individual differences in P-glycoprotein functionality. This may be concluded from the fact that both, morphine and M6G, are substrates of P-glycoprotein [9], an active transporter found at the blood brain barrier. A loss of P-glycoprotein activity caused by genetic polymorphism [10] or by co-administration of P-glycoprotein inhibitors such as cytostatics, calcium channel blocker or cyclosporin A, may result in a roughly doubled brain uptake of M6G [11]. Clinical opioid effects may be enhanced by that mechanism, although this expectation derives so far from studies in vitro [11] and laboratory animals [12], whereas, direct clinical evidence for a significant interaction between morphine and P-glycoprotein inhibitors is still lacking. Experimental P-glycoprotein blockade might furthermore be used to find out whether the long delay between the time course of M6G plasma concentrations and the time course of its effects is relay due to a slow transfer between plasma and effects site.

When developing a dosing regimen in order to achieve the same effect site concentrations of morphine and M6G in all patients, the clinical effect may still vary. Opioid effects depend on concentration-effect relationships that are related to opioid receptor density, opioid-receptor activity, or activity of physiological systems involved in the clinical outcome. Possible, but not yet clinically demonstrated, sources of inter-individual variability are genetic variability of μ-receptor functionality [13], individually different density of splice variants of the μ-receptor [14], or differences in expression of the hypothesized distinct M6G-receptor [15].

2. Current status of PK/PD modeling of the clinical effects of morphine

Clinical pharmacological research on morphine aims at the development of individualized dosing regimens that provide a specific patient with an optimum of morphine analgesia. The need for individualized dosing regimes derives from the inter-individual variability of the pharmacological response to morphine. Population pharmacokinetic–pharmacodynamic (PK/PD) modeling provides a tool to identify the sources of variability, thereby, directing pharmacological research toward explanation of residual variability in order to achieve a complete mathematical model of morphine pharmacology that can serve as a basis of individualized dosing. The currently available data is insufficient to develop a model that achieves optimum dose individualization for morphine. The bases of PK/PD modeling of morphine and M6G have been developed [16,17] but covariate data (Fig. 1) are incomplete. Current knowledge still limits to qualitative data about the impact of renal dysfunction on the opioid effects observed after morphine administration that is mainly caused by M6G accumulation. To this add hints at a decreased morphine clearance in patients with compromised liver function (36, 37). However, there is still no population PK/PD model that quantitatively incorporates this knowledge in order to predict the

clinical outcome in a specific patient, and has to be seen what the rapidly advancing field of pharmacogenomics can provide for morphine dose individualization.

Population pharmacokinetic–pharmacodynamic modeling can help to systematize the complex processes involved in the clinical actions morphine. It can guide the research toward a more complete understanding of the underlying pharmacology. It can furthermore be used as a tool for designing studies on morphine/M6G pharmacology. The mathematical approach allows for simulation of the impact of different possible study designs on the study outcome, and by that way allows for identification of the study design that is most likely to be successful in terms of the specific study aim. Finally, a model of morphine/M6G pharmacology can be found that integrates current knowledge and allows for calculation of morphine dosing regimens that provide an optimum of morphine analgesia to a specific individual.

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Appendix A. Discussion 3

G. Levy: Congratulations on the very nice and comprehensive approach that you used. A couple of points: one has to do with the concentration gradient of a metabolite, plasma to site of action of biophase, in the case where the metabolite 6-glucuronide (M6G) is infused or injected, as opposed to when a precursor is administered and the metabolite is formed near or at the biophase. I think it is an important point, and in my work I have never been disappointed, if I could not match the effect of a metabolite when it is administered in equal concentration under the two conditions. The other point has to do with the complexity of analgesia, when patient controlled analgesia (PCA) is utilized; one finds that when one infuses morphine at a sub-therapeutic rate that produces about half the therapeutic concentration, it has no sparing effect on the rate of administration of morphine by the patient, and that gives me pause about the relationship between morphine, or morphine metabolite concentration, and effect. And finally, do you believe that the 3-glucuronide (M3G) is in fact an antagonist, or is it not?

J. Lötsch: From the literature, there are some studies showing that M3G strongly antagonizes morphine analgesia, even being responsible for morphine tolerance because then it accumulates as M3G. There are also studies telling M3G is not an opioid at all and it acts through other systems, even something to do with blood sugar concentrations. And there are at least as many studies telling M3G has an antagonistic action, as many studies it has no action at all. The present knowledge is not enough to incorporate M3G into the system and we did not try to convince our ethics committee and administrate M3G into humans to look what happens, because we had not got enough data to that.

H.J. McQuay: I am in the embarrassing position that for once I wrote an abstract, and my abstract kind of mocks this approach in general, for the reasons that I am getting old

and we have been round this loop before. I agree with what Gary Levy said. The interpretation of plasma concentration to this area is a nightmare. On the specific thing of the M3G, I think Jörn Lötsch is just being uncritical here. Among the good basic studies, say that M3G has no antagonistic effect through the opioid receptor; at very high concentrations it has non-opioid receptor mediated effects on the CNS. So, I think you have got to be a little more critical in appraising the evidence here and apply a kite-mark of good study and bad study before you jump to these conclusions. On the sparing issue, again we are into very difficult territory including, as has been rediscovered recently, the effects of these opioid infusions in inducing acute tolerance, previously described by Brian Cox in the 1960s.

A. Bye: I think I would share some of Henry's sentiments. The literature is crammed full of work with morphine and its metabolites, and I think that we need to be steered through to the good and away from the bad.

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