Editor—We thank Dahan and Lotsch for their interest in our review and their valuable comments to the discussion about the role of morphine-6-glucuronide (M6G), for the analgesic effect after morphine administration.

Because morphine is used worldwide as the potent standard analgesic drug, with the formation of an even more potent metabolite M6G, it is important to elucidate the relative contribution of morphine and M6G to the overall analgesic effect. In consequence this would enable a scientifically based adaptation of dosing regimens, to patients with conditions such as renal impairment.

Our approach was based on published data on mu-receptor binding, plasma protein binding, concentrations (and area under the concentration-time curve (AUC)) of morphine and M6G in blood or CSF (cerebrospinal fluid), or concentration ratios to calculate free CSF concentration, corrected for receptor binding for each compound. We only used data obtained after morphine administration. Both M6G and morphine do not easily cross the blood-brain-barrier, being substrates of the efflux transporter P-glycoprotein. Other drug transporters such as OATP2 and GLUT-1 are still being discussed. Clinical data of an association of p-glycoprotein polymorphism and morphine-induced adverse events have been reported. On the other hand, inhibition of P-glycoprotein by cyclosporine, increased morphine disposition after i.v. administration by less than 20%; this was accompanied by an enhanced and prolonged miosis. In addition, M6G and morphine-3-glucuronide (M3G) AUC’s were increased by cyclosporine, which could not be explained by a metabolic interaction. The pharmacodynamic model used, did not include potential effects of the morphine glucuronides.

There is a major problem when comparing pharmacodynamic effects observed after morphine administration to the ones observed after M6G administration. M6G has been well characterised in its pharmacokinetics and dynamics when given as a parent drug, no metabolism occurs and hence this is an ideal situation to elucidate the mechanisms behind the pharmacological actions. This is however much different for morphine, which possesses pharmacological potential on its own, but when administered to humans the metabolites M3G and M6G are formed which are present in plasma at 40-fold and seven-fold higher concentrations. Consequently, these three substances are always present together, in plasma and in CSF. However, being substrates of drug transporters there is always the possibility that they influence each other in terms of blood brain barrier penetration. So far this has not been addressed by clinical research. Only one attempt has been made where in a placebo controlled trial, morphine, M6G, and M3G were administered separately and as combinations of morphine and M3G and in the last study arm M3G and M6G. It was shown that M3G was not different to placebo in terms of pharmacodynamic effects, however M6G showed potent analgesic effects with few side effects. The authors conclude that there is still a problem in understanding the relative contribution of M6G, M3G and morphine itself because of the limited information available at the receptor level.

We therefore believe that our approach of using available concentration data from plasma and CSF, after administration of morphine, to elucidate the relative contributions of morphine and its active glucuronide metabolite M6G, to the overall analgesia, taking into account the simultaneous presence of morphine, M6G and M3G is valid. The data obtained from direct assessments of the pharmacokinetics and pharmacodynamics after the administration of M6G itself, can only be extrapolated to the situation after morphine administration with great caution.

Declaration of interest
None declared.

References