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Finding the fine line between pleasure and pain

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There's a very fine line between pleasure and pain. They are two sides of the same coin, one not existing without the other.

—E. L. James, *Fifty Shades of Grey*

It is often said that there is a fine line between pleasure and pain. From a pharmacological point of view, this fine line might be balanced by opioid neurotransmitter pathways. Every anaesthetist knows that the opioid neurotransmitter system plays a central role in pain processing, and that the administration of exogenous opioids reduces the activity in these pathways, thereby attenuating the experience of pain. Most also know that the endogenous opioid system not only mediates the perception of pain, but it also influences affective responses to painful stimuli.[1] Far less well known is the fact that there is some truth in the aforementioned saying, as it appears that the opioid neurotransmitter system also modulates the experience of pleasure. Indeed, the endogenous opioid system can also modulate the affective responses to hedonic stimuli.[2,3]

Opioid analgesics are commonly and routinely used for the treatment of acute or chronic pain; therefore, it is worth considering whether the administration of exogenous opioids might influence the affective responses to pleasurable stimuli. Heiskanen and colleagues[4] investigated this question by serial administration of an opioid receptor agonist (remifentanil), a placebo, and an opioid receptor antagonist (naloxone) to healthy male participants whilst they watched video clips that were either affectively neutral or positive. The authors reported that the participants rated these video clips as more 'pleasurable' whilst they received remifentanil, and concluded that remifentanil mediates pleasure.

This interpretation was the subject of a subsequent correspondence by Leknes and Atlas,[5] who commented on the methods used by Heiskanen and colleagues.[4] It can be uncomfortable or even painful for the authors to have their work commented on, especially when the comments are critical. Few would find it pleasurable. However, a constructive critique of methodological details and experimental results of a study can sometimes stimulate scientific progress that advances the field.

Leknes and Atlas[5] pointed out that methodological standards for psychological and pharmacological experiments should be applied when psychopharmacological studies are performed and evaluated. Amongst several issues, they pointed out the absence of valid control conditions as a weakness in the study of Heiskanen and colleagues.[4] The control condition applied by Heiskanen and colleagues was the administration of a saline solution, but this was within a fixed and single-blind (blind to the participant) schedule. This leaves room for alternative contributions to the reported effect, such as an effect of drug order, time effects, and expectations of the investigator (who was not blinded). Future studies should use a double-blind randomised placebo-controlled design to rule out such confounds. Yet, even when this 'gold standard' randomised double-blinded placebo-controlled study is used, the results should be critically assessed, as other factors besides the pharmacological manipulations might influence the result, such as selection of responders and expectations of participants.[6] Control conditions for the experimental modulation of the opioid system should be particularly critically examined to account for the fact that expectation can also influence activity in the opioid pathways and effects of opioidergic drugs.[7] In the case of remifentanil, Atlas and colleagues[8] have set a useful precedent with a double-blinded study, in which they administered remifentanil or placebo, manipulated the expectations of volunteers, and then studied the influence of opioids and expectation, and the interactions amongst them, on pain experience and on functional MRI-detected changes in brain activity in pain and other networks.

Psychopharmacological research is best performed by an interdisciplinary team to combine expertise from disciplines, such as psychology and pharmacology. A prime example of the potential benefits of such synergies across disciplines is the refinement that can result from the use of pharmacokinetic models to further characterise psychopharmacological effects (e.g. as applied by Atlas and colleagues[8]). Experiments often consider drug washout periods, but the application of multiple compartment models can provide insights into how (estimated) drug concentrations in the brain could influence psychological effects. In the current example, the authors applied target-controlled infusion technology to administer remifentanil at a target effect-site concentration of 1 ng ml^{-1} for 23 min. During the last 20 min of the infusion, when the effect-site and plasma remifentanil concentrations could reasonably have been considered to be at steady state, the subjects watched video

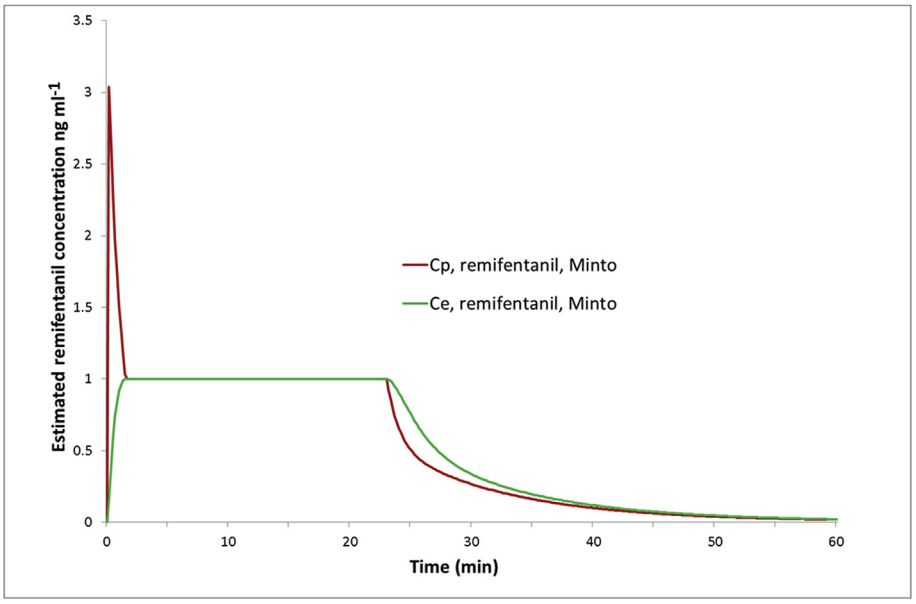

Fig 1. Plasma and effect-site remifentanil concentrations (Minto model estimates) during and after a 23 min infusion at a target concentration of 1 ng ml^{-1}.

clips. After that, the infusion was stopped, and then a 10 min washout period followed before the saline administration phase began. Anaesthetists generally consider remifentanil to be an ultrashort-acting drug, so most would consider a 10 min washout period to be adequate. Pharmacokinetic modelling techniques can help to judge more accurately if this is indeed the case. Figure 1 was produced with data from simulations performed with a function from PKPD tools (pharmacokinetic/pharmacodynamic tools) that uses the model of Minto and colleagues [9,10] to estimate remifentanil concentrations. As the simulation shows, at the start of the saline administration phase, the plasma and effect-site concentrations are still 0.2 and 0.24 ng ml^{-1}, respectively. Even after 17 min, the concentrations are still about 0.1 ng ml^{-1}. It is plausible that these concentrations would influence mood and valence. We would therefore also suggest that future investigators use software, such as PKPD tools or stanpumpR[11] to check the validity of their assumptions, or better still, design studies to determine the thresholds below which remifentanil no longer has any analgesic or mood-altering effects, or does indeed not alter affective responses to painful or pleasant stimuli (if they are different). Such an application of stanpumpR for naloxone infusion has recently been provided by Shafer.[12]

In summary, neuropsychopharmacological studies are complex and necessitate multidisciplinary collaborations. We are grateful to readers, such as Leknes and Atlas,[5] for their correspondence, discussing the strengths and weaknesses of such work, and believe that such constructive discussion helps to advance our understanding of psychopharmacological mechanisms.

Authors' contributions

Manuscript conception/writing: both authors.

Declarations of interest

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