Medical Hypotheses 83 (2014) 326–331

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Oxycodone recycling: A novel hypothesis of opioid tolerance development in humans

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ARTICLE INFO

Article history:
Received 23 April 2014
Accepted 9 June 2014

ABSTRACT

We hypothesize that oxycodone (OC) recycling promotes sustained synaptic OC content, which prolongs OC's exposure to local μ-opioid receptors (μORs). In that way, OC recycling gives rise to OC tolerance in humans.

To pilot test our hypothesis, we developed a whole-body OC mass transport tolerance recovery model. The model derived quantifiable measure of tolerance is T_{Ω}. T_{Ω} estimates OC's tolerance recovery in days; It is defined as the rate of recovery of OC's pharmacologic response after OC is stopped.

We studied a random sample of five opioid intolerant healthy male subjects with no history of opioid or illicit drug use, or comorbidities *in silico*. Subjects were age 24.5 ± 2.3 yr (all values mean ± SD), weight 93 ± 20 kg, and CYP2D6 EM phenotype. Each subject was studied under two experimental conditions: (1) administration of a single oral dose of OC 12 ± 7 mg; and, after complete washout of OC from the intravascular pool, (2) administration of repetitive oral OC doses every 4 h for 5 half-lives ($t_{1/2}$ = 4.5 h)—after which time steady-state was assumed.

Repetitive OC dose T_{Ω} fell 61% compared to single OC dose T_{Ω} (5.2 ± 1.1 vs. 3.5 ± 0.7 days, $p = 0.001$). The fall in T_{Ω} was associated with a significant 3-fold increase in extravascular OC content, which was accompanied by 2-fold increase in OC spillover from the extravascular pool, into the intravascular pool.

Thus, the model predicted that a single dose of orally administered OC could give rise to tolerance. This is consistent with the widely held view of acute opioid tolerance. In addition, the dynamic changes accompanying repetitive OC dosing suggested that local unbound OC gave rise to both higher extravascular OC content and increased OC spillover. This reflects that OC stimulated endocytosis of μORs was accompanied by a reduction in the availability OC responsive neuroeffector cell surface μOR binding sites.

We conclude that our hypothesis extends current concepts of opioid tolerance development to include OC recycling. OC recycling is a novel hypothesis of OC tolerance development in humans.

Background

Oxycodone (OC) is commonly used to treat acute and chronic non-cancer and cancer pain, and pain related with general and orthopedic surgery [1]. However, achieving pain control with OC is sometimes hindered by tolerance [2]. Opioid tolerance requires increased opioid dosing over time to maintain the same level of analgesic efficacy. Tolerance may occur due to pharmacokinetic and/or pharmacodynamic changes over a "prolonged", nonspecific treatment span. Pharmacokinetic tolerance occurs when the OC clearance rate increases through its major elimination pathway by hepatic cytochrome 2D6 or 3A4 isoenzymes. This process can be accelerated or decelerated by concomitant use of foods or

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http://dx.doi.org/10.1016/j.mehy.2014.06.006
0306-9877/

medications that induce or inhibit these enzymes. Increased OC clearance results in a gradual reduction in plasma OC concentrations, while the daily OC dose remains the same. Pharmacodynamic tolerance occurs when OC molecules bind to μ-opioid receptors (μORs) and causes them to down-regulate.

Several authors have advanced hypotheses to explain pharmacokinetic tolerance [3–5]: metabolite production, changes in enzyme activity, and changes in drug transporter function. Similarly, several authors have advanced hypotheses to explain pharmacodynamic tolerance [6–8]: μOR downregulation, μOR endocytosis, μOR binding affinity, μOR functional selectivity, neurotransmitters, and cross-tolerance. However, so far, these hypotheses have not been appreciated for application at the point-of-care to help clinicians make quantifiable decisions about OC dosing in patients.

Ouellet and Pollack [9,10] found that morphine tolerance depends on morphine's systemic drug concentration and exposure time. Since morphine and OC are both phenanthrenes, and therefore structurally similar except for OC's dehydroxylated 6th carbon, we believe opioid tolerance, specifically OC could depend, at least in part, on their concentration and exposure time within the synaptic milieu. This reasoning appeals to the receptor occupancy theory, which maintains that as the concentration of OC in the vicinity of opioid receptors increases, the likelihood of OC binding to these receptors also increases [11,12].

After a comprehensive literature search using PubMed.gov, Scholar.Google.com, and Scopus with search terms entered: opioid tolerance, opioid tolerance mechanisms, opioid tolerance hypothesis(es) and theory(ies), pharmacokinetic opioid tolerance, pharmacodynamic opioid tolerance, μOR opioid tolerance, and the latter terms substituted with morphine and OC, we did not find any study advancing a quantifiable hypothesis of opioid tolerance, in general, or OC tolerance, in particular, that proposes OC recycling as a potential hypothesis for OC tolerance development in humans.

Hypothesis

We hypothesize that OC recycling promotes sustained synaptic OC content, thereby prolonging OC's exposure to local μ-opioid receptors (μORs). In that way, OC recycling produces OC tolerance in humans.

OC tolerance model (a hypothesis)

Current hypotheses describing opioid tolerance only involve μORs. The synaptic milieu is not considered [6]. Our hypothesis is quantifiable, which enables a method to mathematically analyze and experimentally test it. The model diagram illustrated in Fig. 1 represents our hypothesis. Table 1 presents a glossary of symbols. The model is a whole-body OC mass transport tolerance recovery model. The model is divided into three zones: the GI tract, intravascular pool, and extravascular pool.

In this model (Zone 1), the patient takes OC tablets or capsules orally, which enter the gastrointestinal tract and are followed by dissolution, absorption, hepatic first pass, and entrance into systemic circulation. In order to solve the model, we need to first calculate the rate at which OC enters the circulation. We calculated this rate using the following formula [13]:

$$\begin{aligned} input &= \mathrm{CO} \times C_{\mathrm{in}} \\ &= \frac{\text{Bioavailability} \times (\text{Dose}/\tau)}{Cl_{\mathrm{EM}} \times \text{Weight(kg)}} \times 0.001 \\ &\quad \times V_d \ (\text{mg/min}) \end{aligned} \tag{1}$$

where CO (L/min) represents cardiac output calculated using the method of Liljestrand and Zander [14]; critically assessed by Sun and coworkers [15]. The standard deviation of the absolute cardiac output estimation error using this method is 1 L/min and the best relative (uncalibrated) cardiac output estimate has 18% error at one standard deviation. Our calculations were based on relative cardiac output estimates. C_{in} (mg) represents OC content at the inlet of the aortic arch, bioavailability was set to 0.87, the repetitive dosing interval (τ) to 4 h, clearance for CYP2D6 extensive metabolizer phenotype (Cl_{EM}) 0.51 ± 0.13 L/kg/h (0.0085 ± 0.0022 L/kg/min), and apparent volume of distribution (V_d) 2.8 ± 0.9 L/kg. For repetitive oral dosing, the accumulation ratio $(\mathrm{AR}) = 1/1 - e^{-k_e \cdot \tau}$ where k_e is OC's phenotype-specific first-order elimination rate constant equal to 0.1824 ± 0.0380 h^{-1} (0.0027 ± 0.0006 min^{-1}) [13].

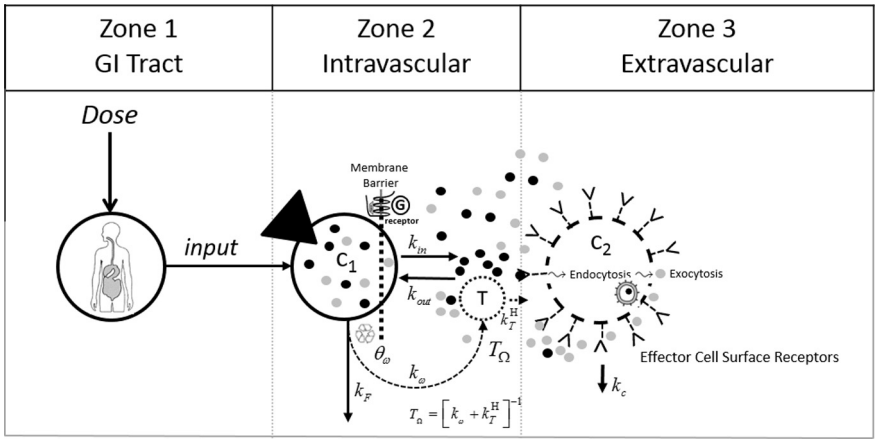

Fig. 1. Oxycodone (OC) whole-body mass transport tolerance recovery model. The model is divided into three zones: the GI tract, intravascular pool, and extravascular pool. The extravascular pool contains the tolerance recovery virtual compartment. This compartment is labeled *T*; it is dotted to indicate that it is a virtual compartment. k_ω denotes the fractional OC mass recycling rate. OC recycling promotes sustained synaptic OC content, which prolongs OC's exposure to local μ-opioid receptors (μORs). In that way, OC recycling gives rise to OC tolerance in humans. T_Ω quantifies OC tolerance recovery in days^{-1}. For each point along the flow path of OC through the model, two different types of OC molecules are identified based on their sites of origin: the black dots represent OC molecules that originate from the dosing compartment ($\mathrm{OC_{DC}}$), and the gray dots represent OC molecules that originate from the extravascular compartment ($\mathrm{OC_{EV}}$). We believe that $\mathrm{OC_{EV}}$ represent $\mathrm{OC_{DC}}$ molecules that diffuse back into the intravascular compartment, from the extravascular compartment; but, they also likely represent intact functional $\mathrm{OC_{EV}}$ molecules released into the synaptic milieu by exocytosis. First, $\mathrm{OC_{DC}}$ bind to μORs on the cell surface, undergo endocytosis, and they are isolated in vesicles coated with clathrin. This mechanism is depicted in the model by an $\mathrm{OC_{DC}}$ molecule binding to a neuroeffector cell surface μOR, its endocytosis and trafficking within the synaptic axoplasm, and its subsequent exocytosis as an intact $\mathrm{OC_{EV}}$ molecule. Furthermore, the model shows $\mathrm{OC_{EV}}$ molecules released into the synaptic milieu by exocytosis become functionally available for "reuse" by μORs. See text for further details.