Pharmacological Research 118 (2017) 64–70

Contents lists available at ScienceDirect

Pharmacological Research

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

Original article

The effect of morbid obesity on morphine glucuronidation

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ARTICLE INFO

Article history:
Received 6 June 2016
Received in revised form 29 August 2016
Accepted 29 August 2016
Available online 5 September 2016

Keywords:
Obesity
Glucuronidation
Morphine
Bariatric surgery
Steatohepatitis

ABSTRACT

The purpose of the present work was to study the change in morphine metabolic ratio in obese subjects before and after Roux-en-Y Gastric Bypass (RYGB) and to identify clinical and/or biological factors associated with this change. The pharmacokinetics (PK) of oral morphine (30 mg), morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) was performed in patients before (n = 25; mean BMI = 43.2 (35.4–61.9) kg/m^2), 7–15 days (n = 16) and 6 months after RYGB (n = 19; mean BMI = 32.3 (25.4–46.0) kg/m^2). Morphine C_{max} and $AUC_{0\text{-inf}}$ were significantly increased and morphine T_{max} significantly shortened at 6 months after RYGB compared with preoperative data, indicating an important increase in the rate and extent of morphine absorption. The morphine metabolic ratio $_{0\text{-inf}}$ M3G + M6G/Morphine, decreased significantly from the preoperative to 6 months postoperative period with an average of −26% (range −74%; +21%; p = 0.004), but not in the immediate post-operative period. The change in morphine metabolic ratio was associated with a change in BMI, fat mass in kg, and triglyceride levels (rho = 0.5, $p \leq 0.04$). The degree of change in several markers of low-grade inflammation, or the level of liver steatosis and fibrosis before surgery, was not associated with the change in morphine metabolic ratios. Our findings indicate that RYGB-induced weight loss significantly decreases morphine metabolic ratio, arguing for an effect of morbid obesity on glucuronidation. With glucuronide exposure at 6 months similar to preoperative values, a higher morphine $AUC_{0\text{-inf}}$ should encourage reducing morphine dosage in patients undergoing RYGB and chronically receiving immediate-release oral morphine.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the plasma concentration–time curve; BMI, body mass index (BMI); C_{max}, maximum plasma concentration; CRP_{us}, ultrasensitive C-reactive protein; GGT, gamma-glutamyl transferase; HNF-1alpha, hepatocyte nuclear factor-1alpha; HOMA-IR, homeostasis model assessment of insulin resistance; IL6, interleukine-6; k_e, terminal elimination phase; LC–MS/MS, liquid chromatography mass spectrometry in tandem; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetics; RYGB, Roux-en-Y gastric bypass surgery; T_{max}, time to reach C_{max}; UGTs, UDP-glucuronosyltransferases.

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http://dx.doi.org/10.1016/j.phrs.2016.08.031
1043-6618/

1. Introduction

Glucuronidation is an important metabolic pathway for many small endogenous and exogenous lipophilic compounds; glucuronidated products are usually inactive and water-soluble, thus facilitating their excretion from the body into the bile and/or urine [1].

Glucuronidation is catalyzed by UDP-glucuronosyltransferases (UGTs) [2]. UGTs are highly expressed in the liver where they play a major role in hepatic clearance through glucuronidation of their substrates [3,4]. UGT mRNAs have also been detected in over 20 extrahepatic tissues such as the gut, the kidneys and adipose tissues [5]. The extrahepatic glucuronidation activity helps to maintain homeostasis and hence regulates the biological activity of endogenous molecules that are primarily inactivated by UGTs [4,6]. Obesity is one of the various factors that have been shown to increase UGT activity in mice and in humans [7,8].

UGT2B7 is the main human UGT involved in the formation of morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Sixty percent of an oral dose of morphine is glucuronidated into M3G, and 6–10% into the active metabolite M6G [9]. Like morphine, M6G has been shown to be relatively more selective for mu-receptors than for delta- and kappa-receptors while M3G does not appear to compete for opioid receptor binding. M6G is a key determinant of morphine benefit/risk balance. The analgesic effect is even mainly caused by M6G instead of morphine itself, irrespective of the route of administration [10]. The accumulation of M6G in renal failure is associated with an increased incidence of morphine-like side effects (respiratory depression, nausea, vomiting), whereas the exact role of M3G and other metabolites is still controversial, but might include development of morphine-resistant pain, allodynia, and tolerance [11]. The major elimination route for M3G and M6G in subjects with normal renal function appears to be renal excretion [9]. Therefore, all mechanisms (drug-drug interactions, diseases) leading to changes in M6G and M3G plasma levels by changing their production, tissue distribution and elimination may drastically change the benefit/risk profile of morphine.

The factors leading to the variability in morphine requirement and metabolism remain poorly understood [9]. We previously reported results from a longitudinal study describing the effect of the Roux-en-Y gastric bypass surgery (RYGB) and its associated weight loss, on the oral PK of morphine [12]. We showed that RYGB increased the rate at which oral morphine was absorbed, and, to a lesser extent, the morphine area under the curve (AUC) in comparison with the preoperative period [12]. Recently, we showed that patients before RYGB exhibited higher morphine metabolic ratios than those reported in various but non morbidly obese subjects after oral administration of morphine, suggesting an increased morphine glucuronidation in morbid obesity [13].

The purpose of the present work was to study the change in morphine metabolic ratio with weight loss in obese patients undergoing RYGB and to identify clinical and/or biological factors associated with this change.

2. Material and methods

2.1. Study population

Thirty obese volunteers involved in a medico-surgical obesity management program (Department of Nutrition, Pitié-Salpêtrière hospital, Paris, and Department of Digestive and metabolic surgery, Ambroise Paré hospital, Boulogne-Billancourt, France) and candidates for a RYGB were included in the Obesity and morphine (OBEMO) clinical study [12]. Subjects with previously diagnosed diabetes, renal or hepatic dysfunction, untreated obstructive sleep apnea syndrome, those usually treated with sedative or analgesic drugs or with a history of allergy to morphine or opioids were not included. All subjects gave their written informed consent. The protocol "OBEMO study" was approved by the Ethics Committee of Paris, France (CPP Ile de France I) and registered at the ClinicalTrials.gov website (EudraCT number 2009-010670-38, NCT00943969).

In this work, the plasma remaining from our previous study was used to determine morphine, M3G and M6G concentrations. A sufficient amount of plasma was available for 25 subjects before surgery, 16/25 subjects immediately thereafter and 19/25 subjects 6 months after surgery [12].

2.2. Preoperative, peroperative and postoperative clinical and biological data

The preoperative and 6 months' postoperative tests included a clinical chemistry check-up focusing on liver and renal function (aspartate aminotransferase, AST; alanine aminotransferase, ALT; gamma-glutamyl transferase, GGT) and serum creatinine assessment, inflammatory markers (interleukine-6 (IL6), ultrasensitive C-Reactive Protein (CRP_{us}), orosomucoid) [14]. We estimated insulin resistance using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index: insulinemia (mUI/L) × fasting blood glucose (mmol/L)/22.5.

Body composition was estimated by whole-body fan-beam dual-energy x-ray absorptiometry scanning (Hologic Discovery W software, version 12.6; Hologic Inc) before surgery and 6 months after surgery. Body fat mass distribution was determined as described elsewhere [15].

Liver biopsies were obtained during gastric surgery and were formalin-fixed and paraffin-embedded. Serial sections were stained. Minimal set of staining included Haematoxilin and Eosin, PicroSirius Red and Perls staining. Liver sections were graded by adding three sub-scores for lobular inflammation (classified 0–2 or 3), portal inflammation (classified 0, 1 or 2) and fibrosis (classified 0, 1a, 1b, 2, 3 or 4) [16]. Absence or presence of Nonalcoholic steatohepatitis (NASH) in morbid obesity was evaluated according to the Steatosis Activity Fibrosis (SAF) score: normal, score 0; steatosis, score 1 and NASH score 2; as described by Bedossa et al. [17]. Finally, the collection of the different clinical and biological data aimed to test different hypothesis stated in a previous review where for explaining morphine PK differences between obese and non obese subjects [9].

2.3. Oral morphine and glucuronides PK study

2.3.1. Study design

A morphine and glucuronides PK study was performed three times during the study: before surgery (30–7 days before surgery), shortly after surgery (7–15 days after surgery), and 6 months after surgery. Each patient fasted overnight before being given a single oral dose of morphine sulphate solution (30 mg; Oramorph 5 mL, Roxane Laboratories, Inc, Columbus, Ohio). The morphine plasma levels were measured in blood samples taken over the 12 h post dose (0 h, 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h). Additional samples were taken for some subjects during the first two hours. Plasma samples were separated and frozen at −80 °C.

2.3.2. Morphine, M3G and M6G quantification in plasma

Morphine and its major metabolites (M3G and M6G) were quantified in plasma by a previously validated method using liquid chromatography mass spectrometry in tandem (LC–MS/MS) following solid phase extraction as described previously [13]. Chromatographic separations were performed on a LC system (Accela system, Thermo Fisher) with Hypersil Gold® (Thermo Fisher) C18