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Pharmacology of Morphine in Obese Patients

Clinical Implications

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Contents

Abstract

Morphine is an analgesic drug used to treat acute and chronic pain. Obesity is frequently associated with pain of various origins (e.g. arthritis, fibromyalgia, cancer), which increases the need for analgesic drugs. Obesity changes drug pharmacokinetics, and for certain drugs, specific modalities of prescription have been proposed for obese patients. However, scant data are available regarding the pharmacokinetics and pharmacodynamics of morphine in obesity. Prescription of morphine depends on pain relief but the occurrence of respiratory adverse effects correlates with obesity, and is not currently taken into account. Variations in the volume of distribution, elimination half-life and oral clearance of morphine, as well as recent advances in the respective roles of drug-metabolizing enzymes, catechol-*O*-methyltransferase and the μ opioid receptor in morphine pharmacokinetics and pharmacodynamics, may contribute to differences between obese and non-obese patients. In addition, drug-drug interactions may alter the disposition of morphine and its glucuronide metabolites, which may either increase the risk of adverse effects or reduce drug efficacy.

Obesity is recognized as a major public health problem worldwide. The WHO estimates that 400 million people were obese in 2005. In 2015, the number of obese adults is expected to reach 700 million and the number of those overweight, approximately 2.3 billion.[1] The prevalence of obesity (body mass index [BMI] >30 kg/m^2) doubled in the US between 1980 and 2002 in adults older than 20 years.[2] Similar trends are observed in Europe, where the prevalence of obesity exceeds 20% in certain countries.[3] In the US, one out of 20 obese subjects is morbidly obese (BMI >40 kg/m^2), and in Europe too, the prevalence of morbid obesity dramatically increased between 2000 and 2006.[2,4]

Obesity is associated with a high prevalence of pain, due to the increased prevalence of many chronic diseases (including musculoskeletal diseases and cancer) and with poor health status and poor quality of life.[5] An effective treatment for pain is therefore of paramount importance for a substantial number of patients, especially during weight loss management and cardiovascular disease prevention. Moreover, morphine is commonly used in the treatment of cancer pain, and the prevalence of cancer is higher in obese than lean subjects.[6] In the series of obese patients reported by Raebel et al.,[7] 21% used narcotic analgesics for pain.

The use of narcotic analgesics in obesity is particularly difficult because it has been shown that adverse effects are more frequent in obese populations; thus, the incidence of postoperative nausea and vomiting was 65% in obese patients compared with 35% in non-obese patients in a study involving 1181 subjects. Of the 98.1% of patients who were over 17 years of age, 3.6% were obese and 29% were overweight.[8] It is hard to determine a morphine dosage regimen that provides adequate pain relief, as morphine may lead to severe adverse effects, including respiratory depression.[9] Obesity increases the potential for respiratory depression with sleep apnoea syndrome, respiratory failure and the use of sedative medications. Hence, obese patients are at higher risk of admission to an intensive care unit after surgery, and seem to be at higher risk of morphine adverse effects.[10] Variability in opioid-induced antinociception has also been reported in the morbidly obese after surgery, and the 10-fold variation observed in opioid requirements was not related to body surface area, sex, age, dose per injection or anaesthetic agent.[11]

The use of morphine in obesity therefore raises several questions, such as whether the adequate initial dosage should be adjusted to the actual or ideal bodyweight (IBW), and whether, in obesity, the influence of bodyweight, and the respective effects of fat and lean mass, gastric bypass, pharmacogenetics, pain sensitivity and potential drug-drug interaction are due to the increased number of medications prescribed or to the variability of morphine disposition.[7,12] Better knowledge of the potential differences in morphine metabolism in obese compared with lean subjects could help to identify the adequate balance between pain control and the avoidance of sedative or respiratory depressant adverse effects. The aim of the present review is therefore to address different aspects of morphine metabolism and drug-drug interactions involved in the wide intra- and interindividual variability of analgesia and opioid-induced toxicity in morbidly obese patients.

1. Pharmacokinetics and Pharmacodynamics of Morphine in Normal-Weight Subjects

1.1 Pharmacokinetics: Absorption, Distribution, Metabolism and Excretion of Morphine

After oral administration, morphine is almost completely absorbed by the gastrointestinal tract.[13] In animals, the fastest absorption of morphine takes place in the medium of the jejunum and duodenum rather than in the stomach.[14] The pharmacokinetics of morphine and its main glucuronide metabolites are in particular driven by their interaction with both drug transporters and drug-metabolizing enzymes, which may be responsible for their pharmacokinetic interindividual variability. Several drug transporters are located in several healthy tissues, such as the liver, small intestine, kidneys and several barriers such as the blood-brain barrier (BBB), and are involved in the pharmacokinetics of drugs. With drug-metabolizing enzymes, they may reduce oral bioavailability of drugs that are substrates either by effluxing them out of the gut or by eliminating them into the bile during the hepatic first-pass.[15-17] Although morphine is a well known substrate of the drug efflux transporter P-glycoprotein (P-gp), the influence of P-gp on its oral absorption needs to be ascertained since morphine is well absorbed by the gastrointestinal tract. P-gp is richly expressed in the intestine but its impact on the *in vivo* oral absorption is difficult to measure.[15,18] Nevertheless, Kharasch et al.[19] have reported increased absorption of oral morphine in patients receiving quinidine, a well-known P-gp inhibitor, suggesting that intestinal and biliary P-gp may affect absorption and systemic exposure of oral morphine. Among the various members of the multidrug resistance protein (MRP) [ABCC] transporter family, MRP2 (ABCC2) and MRP3 (ABCC3) actively transport morphine glucuronides. However, the role of MRP2 in counteracting intestinal absorption of drugs is limited and it appears to play a more significant role in efflux of chemicals

from the systemic circulation into the bile rather that an absorptive barrier.[17,20] Most drug metabolism occurs within the liver and, to a lesser extent, the proximal small intestine, where drug metabolizing enzymes are also located.[21] Morphine is primarily metabolized in the liver by uridine diphosphate glucuronosyltransferase (UGT) enzymes, and has a specific affinity for the UGT2B7 isoenzyme. UGT, a phase II metabolism enzyme family with several isoforms, has been found to be active in the liver, kidneys and epithelial cells of the lower intestinal tract and more recently in the brain.[22] Sixty percent of an oral dose of morphine 20–30 mg is glucuronidated to morphine-3-glucuronide (M3G), and 6–10% to morphine-6-glucuronide (M6G).[23,24]

Morphine pharmacokinetics after a single dose in normal-weight subjects are summarized in table I.[13,19,25-27] Hasselström and Säwe[27] reported oral bioavailability of 29.2 ± 7.2% after administration of a single oral 20 mg dose of morphine to seven healthy subjects, whereas others studies have pointed towards the important variability in morphine oral bioavailability from 15% to 64%.[25,26]

M6G has a very different distribution, metabolism and excretion profile than that of morphine. Using a three-compartment model, Romberg et al.[28] reported the pharmacokinetic parameters after an M6G bolus dose of 0.3 mg/kg in a homogenous group of healthy subjects.[28] In comparison with intravenous morphine, the volume of distribution (V_d) of M6G was smaller by a factor of about 10 (0.20 L/kg). The smaller V_d of M6G as compared with morphine indicates that M6G distributes less well than morphine into tissues, probably related to its lower lipophilicity as compared with morphine.[28] In addition, the interindividual variability in the V_d of M6G is smaller than that of morphine, with the coefficient of variation ranging from 11% to 30%.[28]

In healthy subjects, Kharasch et al.[19] reported pharmacokinetic data on oral morphine disposition (oral morphine sulphate 30 mg): the time to reach the maximum concentration (t_{max}) was 1.1 ± 0.8 hours, the maximum concentration (C_{max}) was 16.9 ± 7.4 ng/mL, the area under the plasma concentration-time curve (AUC) was 40.8 ± 14.1 ng • h/mL and the terminal elimination half-life ($t_{½}$) was 2.1 ± 0.6 hours.[19] Similarly, Hoskin et al.[25] compared the pharmacokinetic parameters after intravenous (5 mg) and oral (10 mg) morphine, respectively; the average t_{max} ranged from 0.25 to 1.0 hour for the oral morphine, whereas the C_{max} ranged from 274 to 574 ng/mL after intravenous morphine and from 3.9 to 16.4 ng/mL after oral morphine, the AUC ranged from 74.7 to 107.0 ng • h/mL after intravenous morphine and from 11.9 to 46.5 ng • h/mL after oral morphine, and the $t_{½}$ ranged from 1.5 to 2.5 hours after intravenous morphine administration.[25] However, a pronounced interindividual variability in the $t_{½}$ of morphine was previously reported.[26,29-32]

The mean plasma AUC values for M6G were 209.0 ± 27.6 and 183.7 ± 20.2 ng • h/mL after oral and intravenous morphine administration, respectively.[25] When morphine was given orally to patients with normal renal function, the mean M3G/morphine AUC ratio was 24.3 ± 11.4 while the M6G/morphine

Table I. Summary of pharmacokinetic parameters after a single dose of morphine in non-obese subjects[a]

Study and subjects	Dose of morphine	Route of administration	V_d (L/kg)	$t_{½}$ (h)	CL (L/h/kg)	F (%)	C_{max} (ng/mL)	t_{max} (h)
Lötsch et al.[13] (n = 5)	0.14 mg/kg	IV			133.4 (26.4)[b]	34 (9)		
	90 mg	PO (MST)						
Kharasch et al.[19] (n = 12)	30 mg	PO (IR)		2.1 (0.6)			16.9 (7.4)	1.1 (0.8)
Hoskin et al.[25] (n = 6)	5 mg	IV		1.9 (0.2)	1.4 (0.24)	23.8 (4.9)	340.2 (47.3)	0.75
	10 mg	PO (IR)					10.6 (2.15)	
Säwe et al.[26] (n = 7)	0.037–0.066 mg/kg	IV	2.08 (1.18)	3.1 (2.3)	0.55 (0.25)	38.2 (17.1)		
	0.231–0.495 mg/kg	PO (IR)		3.4 (1.93)				
Hasselström and Säwe[27] (n = 7)	5 mg	IV	2.9 (0.8)	15.1 (6.5)	1.2 (0.2)	29.2 (7.2)		
	20 mg	PO (IR)						

a Values are expressed as mean (SD).

b L/h.

CL = apparent total body clearance; **C_{max}** = maximum plasma concentration; **F** = absolute bioavailability; **IR** = immediate release; **IV** = intravenous; **MST** = morphine sulphate, $5H_2O$ sustained-release tablet, equivalent to MST 90 mg; **PO** = oral; **$t_{½}$** = terminal elimination half-life; **t_{max}** = time to reach the C_{max}; **V_d** = volume of distribution.

ratio was 2.7 ± 1.4.[26] The $t_{½}$ values of morphine, M3G and M6G reported by Hasselström et al.[23] were 15.1 ± 6.5 hours, 11.2 ± 2.7 hours and 12.9 ± 4.5 hours, respectively.

The mean systemic plasma clearance of morphine reported by Hasselström and Säwe[27] was 21.1 ± 3.4 mL/min/kg (1.27 ± 0.20 L/h/kg), in agreement with other studies.[23,25,26,28] The clearance values of morphine to form M3G and M6G were 57.3% and 10.4%, respectively, and renal clearance represented 10.9% of total systemic plasma clearance.[27] The major route of elimination for M3G and M6G in subjects with normal renal function appeared to be renal excretion and was influenced by renal function.[33-35] The increased polarity of both morphine glucuronides relative to the parent aglycone limits their diffusion through biological membranes, and it has been suggested that specific transporters may mediate their transport.[36,37] MRP2 and MRP3 may play a role in the urinary elimination of M3G and M6G.[36,38]

More than one-fifth of a dose (20.8%) remained as unidentified residual clearance and pharmacokinetic parameters reported by Hasselström and Säwe[27] are highly suggestive of enterohepatic cycling. MRP2 is localized both at the apical side of enterocytes and at the canalicular membrane of hepatocytes and thus may be responsible for biliary and intestinal secretion of the predominant inactive morphine metabolite M3G, as recently shown in knockout mice.[17,20,39] Interestingly, in the study by van de Wetering et al.,[39] the loss of biliary M3G excretion in MRP2 knockout mice resulted in its increased sinusoidal efflux from hepatocytes to blood and prolonged exposition in plasma that could be attributed to its transport into the bloodstream by MRP3, which is exclusively expressed at the basolateral membrane of hepatocyte.[39] Indeed, MRP3 can easily transport M3G and M6G from the liver into the bloodstream, as recently shown using *in vitro* and MRP3 knockout mice studies.[39]

To date, not much information has been available about the physiological function of MRP3 and MRP2 and their role in the pharmacokinetics and pharmacodynamics of morphine in humans. In conclusion, all of these pharmacokinetic studies pointed out that at least three ABC transporters (P-gp, MRP2 and MRP3) and one drug-metabolizing enzyme (UGT2B7) may be determining factors affecting the pharmacokinetics of morphine and its glucuronide metabolites.

1.2 Morphine Pharmacodynamics

To be a potent opioid agonist, morphine must penetrate the BBB to reach the brain parenchyma, but its penetration is rather limited compared with that of many other drugs, although it permeates the BBB well.[40] The relatively poor brain penetration of morphine has been linked to its active efflux from the brain to the blood by the P-gp at the BBB.[41] Furthermore, a significant negative correlation between the analgesic effects of morphine and P-gp expression in the cortex was recently reported in mice.[42]

M3G lacks analgesic properties, but M6G is an effective analgesic, and might have a more favourable adverse effect profile than morphine, causing less nausea and respiratory depression.[24,43-45] Studies in animals suggested that M3G is a functional antagonist of the antinociceptive effects of morphine and M6G, possibly due to its interaction with receptors other than the known opioid receptors.[46] When we consider the blood-effect site equilibration half-life ($t_{½ke0}$), human studies indicate that M6G equilibrates slowly with the postulated effect-site within the CNS. Romberg et al.[28] reported a mean $t_{½ke0}$ of 6.2 (3.3) hours in 20 healthy subjects receiving intravenous M6G 0.3 mg/kg in a study evaluating pain tolerance with increasing transcutaneous electrical stimulation. In comparison, Lötsch et al.[13] measured the central opioid effect using the pupil size in eight healthy subjects who received morphine 0.5 mg as a loading dose followed by 10.7 mg as an infusion over a period of 4.7 hours, and M6G 10.2 mg as a loading dose followed by M6G 39.1 mg given over a period of 3.7 hours. The estimated median $t_{½ke0}$ of M6G was 6.4 hours, and that of morphine was 2.8 hours. In another study, significant differences in pharmacodynamics between ten men and ten women receiving intravenous morphine (a 0.1 mg/kg bolus dose followed by an infusion of 0.030 mg/kg/h for 1 hour) were observed.[47]

Meineke et al.,[37] who studied morphine, M3G and M6G transfer from the central compartment into the cerebrospinal fluid in a population of neurosurgical patients after an 0.5 mg/kg intravenous administration of morphine over 30 minutes, found that transfer of the metabolites M3G and M6G was slower than that of morphine, as the maximum concentrations occurred at 417 minutes and 443 minutes for M3G and M6G, respectively, compared with 102 minutes for morphine. The brain uptake of M6G measured in the rat, killed 30 minutes after a morphine intravenous injection, was 32-fold lower than that of morphine in an *in vivo* study, and the BBB permeability surface area product of M6G was 57-fold lower than that of morphine.[48] The investigators reported that the liposolubility of M6G was 187-fold lower than that of morphine.[48] Brain uptake in rats was also measured by the internal carotid perfusion technique and after intravenous bolus injections; the BBB permeability to M6G was 32-fold lower than that of morphine.[49] The rate of M6G through the BBB is generally assumed to be slower than that of morphine because

of the hydrophilic nature of M6G.[48,49] The poor BBB permeability to M6G combined with the high concentrations of M6G found in the brain have not yet been explained.[48-50] GLUT-1 and a digoxin-sensitive transporter (probably organic anion transporting polypeptide-2 [OATP2] or SLCO1B1) may be involved in the M6G transport.[50] In addition, MRP2 has been found in human cerebral endothelial cells in patients with refractory epilepsy but the presence of MRP2 at the healthy BBB is still debated since it has not been found by immunofluorescence in human brain vessels from patients with different brain pathologies.[51,52]

Morphine, as well as M3G and M6G, has an affinity primarily for the μ opioid receptor, a product of the opioid receptor mu 1 (*OPRM1*) gene and, to a lesser degree, for the κ and the δ opioid receptors. M6G might have a lower affinity for the μ and the κ opioid receptors than morphine, but may have slightly higher analgesic efficacy and might induce fewer respiratory adverse effects than morphine.[45,53] The μ opioid receptor modulates the responses to mechanical, chemical and thermal nociception at the supraspinal level, and the κ opioid receptor modulates spinally mediated thermal nociception and chemical visceral nociception. Following inflammation, μ opioid receptors are found at the periphery of pre- and postsynaptic sites in the dorsal horn of the spinal cord, and in the brainstem, thalamus and cortex, which together constitute the ascending pain transmission system.[54] In addition, μ opioid receptors are found in the midbrain periaqueductal grey substance, the nucleus raphe magnus and the rostral ventral medulla, where they constitute a descending inhibitory system that modulates spinal cord pain transmission.[55] At the cellular level, opioids reduce calcium ion entry, thus also reducing the release of presynaptic neurotransmitters such as substance P, which is released from primary afferents in the dorsal horn. They also enhance potassium ion efflux, resulting in the hyperpolarization of postsynaptic neurons and a decrease in synaptic transmission. A third mechanism of opioid action is the inhibition of GABAergic transmission in a local circuit (e.g. in the brainstem, where GABA inhibits the action of a pain-inhibitory neuron). This disinhibition of the action of the dopamine system causes dopamine release in the nucleus accumbens and has the net effect of exciting a descending inhibitory circuit.

The opioid receptors are part of the endogenous opioid system, which includes a large number of endogenous opioid peptide ligands. Three distinct families of classical opioid peptides have been identified: the enkephalins, endorphins and dynorphins.[56] The physiological roles of the endogenous opioid peptides are not completely understood. They appear to function as neurotransmitters, neuromodulators and, in some cases, neurohormones. They play a role in some forms of stress-induced analgesia and constitute part of an endogenous pain modulatory system. In addition, catechol-*O*-methyltransferase (COMT), an enzyme metabolizing catecholamines, has recently been implicated in the modulation of pain. Low COMT activity leads to increased pain sensitivity via a β_2- and β_3-adrenergic mechanism.[57]

The individual variability of opioid pharmacology suggests that genetic factors may influence the response to opioids. This view is strongly mediated by observations of variation among ethnic groups with respect to the opioid response.[58,59]

Interindividual variability in morphine efficacy can be related to variations in the interaction between M6G and the μ opioid receptor.[58] The genetic complexity of the *OPRM1* gene was shown by Hoehe et al.,[60] who identified 43 allelic variants. Their consequences have been studied in healthy subjects.[61,62] The frequency of the most common single nucleotide polymorphism (SNP), A118G, is about 10–14% in Caucasians.[60] This polymorphism has been associated with reduced opioid effects and can lead to the need for 2- to 4-fold higher concentrations of alfentanil to control pain, and for 10- to 12-fold higher concentrations to obtain respiratory depression compared with the wild-type allele in healthy subjects.[63,64] In studies enrolling cancer patients, homozygous carriers for 118G required about twice as much morphine as those homozygous for the wild type A118 allele to achieve adequate pain relief.[65-67] Human subjects with one or two 118G copies exhibited decreased papillary constriction after M6G administration, while the 118G variant may be protective against M6G toxicity.[68,69] The A118G SNP of the *OPRM1* gene and C3435T SNP of the human *ABCB1*/*MDR1* exert strong but independent effects on responsiveness and pain relief, but not on the occurrence of adverse effects.[67] Other recently identified variants have not been found to influence morphine efficacy. Among cancer patients, homozygous carriers of both 118G *OPRM1* and 158Met *COMT* allelic variants required the lowest morphine dose to achieve pain relief.[64,70]

Recent reports have suggested that Val158Met, a functional polymorphism of the *COMT* gene, partially influences cognitive performances, some psychiatric affections, fibromyalgia, experimental pain sensitivity and morphine efficacy in cancer pain treatment morphine requirements.[57,71-76] Functional polymorphisms in the *COMT* gene result in 3- to 15-fold reductions in *COMT* activity.[57,73-76] Lower COMT activity is associated with heightened pain sensitivity.[77] The frequency of the 158Met allelic variant, associated with lower activity of COMT, is about 50% in Caucasians, 18% in Han Chinese and 29% in Japanese.[77-79] In addition, among patients

Table II. Proteins involved in the control of nociception

Protein	Gene	Role
μ opioid receptor	*OPRM1*	Mediates endorphin effects in the physiological pain protective system
δ_1 opioid receptor	*OPRD1*	Mediates enkephalin effects in the endogenous opioid system
Catechol-*O*-methyltransferase	*COMT*	Degrades cathecholamines and mediates adrenergic, noradrenergic and dopaminergic neuronal transmission
Transient receptor potential cation channel	*TRPV1*	Mediates pain induced by heat or capsaicin
Transient receptor potential cation channel subfamily A	*TRPA1*	Mediates cold sensation and pain
Fatty acid amide hydrolase	*FAAH*	Degrades the fatty acid amide family of endogenous signalling lipids, including the endogenous cannabinoid anandamide, involved in the suppression of pain
GTP cyclohydrolase 1	*GCH1*	Contributes to the regulation of biogenic amine and nitric oxide synthesis
IL-1 receptor antagonist	*IL1RN*	Competitive inhibitor of IL-1 bioactivity
IL-1α	*IL1A*	Cytokine-inducing apoptosis
IL-1β	*IL1B*	Cytokine involved in the inflammatory response and in a variety of cellular activities, including cell proliferation, differentiation and apoptosis

GTP = guanosine triphosphate; **IL** = interleukin.

with cancer who received morphine, another allelic variation in the COMT enzyme (a SNP in intron 1 (-4873G) present in 10.4% of the population) was independently associated with central adverse effects.[80]

In addition, it is well known that the response to painful stimuli varies between individuals and this could be the consequence of individual differences to pain sensitivity that may be related to genetic factors. The proteins involved are briefly reported in table II.

2. Pharmacokinetics and Pharmacodynamics of Morphine in Obese Subjects

2.1 Clinical Observations

Interindividual variability in opioid pharmacology leading to variability in dose requirements for pain relief was observed in an obese population who used patient-control anaesthesia (PCA).[11] In a sample of 1181 patients using PCA, more obese than non-obese patients experienced postoperative nausea and vomiting.[8] Furthermore, in a post-anaesthesia care unit, obesity was significantly associated, over a period of 33 months, with a larger number of critical respiratory events than in non-obese subjects, in a cohort of 24 157 consecutive patients given a general anaesthetic.[10] In this cohort, anaesthetic risk factors ($p < 0.05$) included, among others, opioids used in premedication (odds ratio = 1.8) and fentanyl used in combination with morphine (odds ratio = 1.6). These observations raise questions concerning opioid pharmacokinetics and morphine pharmacodynamics in obese populations.

Drug concentration and elimination rates depend on metabolic activity and interindividual variability in metabolism affects drug action. We review the factors involved in the variability of metabolism and the efficacy of morphine and study them in the case of obese subjects. They are summarized in table III.

2.2 Drug Absorption and Consequences of Bariatric Surgery

Absorption of drugs does not appear to be significantly modified in the presence of obesity.[133] Genetic factors and drug-drug interactions may constitute a source of interindividual variation in drug transporter and drug metabolizing enzymes, and thus in oral bioavailability.

Little is known about the consequences of bariatric surgery on intestinal absorption of drugs, especially that of morphine.[88,89] Drug solubility, the surface area of drug absorption and gastrointestinal blood flow may affect oral drug bioavailability. Most drugs are absorbed in the jejunum rather than in the stomach, duodenum or ileum, whereas drug efflux, especially P-gp-mediated efflux, occurs mainly in the ileum and the colon. Conversely, MRP2-mediated efflux seems to occur all along the small intestine.[134-137] Tablets and capsules must disintegrate and dissolve before absorption, and the time required for disintegration and dissolution affects the amount of drug absorbed and/or the rate of its absorption. Once a drug is solubilized, it is absorbed through the jejunum epithelium by paracellular and/or transcellular passive diffusion or active uptake transport. Drugs in aqueous solutions are more rapidly absorbed than those in oily solutions, suspensions or solid

form. Half of the total mucosal area is found in the proximal quarter of the gut, which has the greatest capacity for drug absorption.[138]

Roux-en-Y gastric bypass is one of the most frequently performed surgical techniques and combines restrictive and malabsorptive procedures. A 30–60 mL pouch is created at the top of the stomach to restrict food intake. The small intestine is cut by 45–150 cm from the stomach, and the intestine is connected to the pouch at the top of the stomach. The small pouch produces much less hydrochloric acid than the entire stomach. Subsequently, this increase in gastric pH may affect drug absorption of medications that depend on drug ionisation.[139] For instance, it increases absorption of weak bases such as ketoconazole.[140-142] When there is a reduction in the total intestinal surface area for absorption, drugs with long absorptive phases may have decreased bioavailability.

It is, however, possible that mechanisms for compensatory absorption by other sites intervene, although this requires confirmation. The stagnation of weight loss after bypass may account for such an adaptative mechanism of the intestinal barrier to nutrient malabsorption, but whether or not these modifications also impact on drug absorption has never been tested, to the best of our knowledge. Drug pharmacokinetics before and at different times after surgery may be helpful to describe such an adaptive mechanism of the remaining small intestinal mucosa.

Bariatric surgery may also increase the risk of adverse drug effects due to removal of the epithelial intestinal barrier.[18] Because of its extensive glucuronidation by UGT2B7, which is expressed in the small intestinal mucosa, morphine absorption may be modified after bariatric surgery.[143] In the very few studies including patients who had a jejunoileal bypass, phenazone absorption and hepatic drug metabolizing capacity appeared to be unaffected for up to 57 months after intestinal shunting.[90] No permanent effect on the rate or amount of sulfisoxazole absorption was observed after intestinal bypass surgery in four morbidly obese women (110–150 kg).[144] However, unlike morphine, these drugs do not undergo intestinal first-pass. Therefore, it would be clinically relevant to describe the consequences of gastric bypass on morphine systemic exposure and pharmacodynamics in obese patients.

Table III. Putative factors between obese and normal-weight subjects that may affect morphine pharmacokinetics and pharmacodynamics

Pharmacokinetics
Absorption
Genetic factors
Intestinal flora[81]
Drug-drug interactions[29,82-87]
Bariatric surgery[88-90]
creation of a 30–60 mL pouch
increase in gastric pH
reduction in the total intestinal surface area
Distribution
Increased adipose tissue and lean body mass[91]
High cardiac output[92-94]
Increased total body water[91,95-97]
Expansion of the extracellular compartment relative to the intracellular compartment[97-99]
Higher hydration of the fat-free mass[92]
Metabolism
Genetic factors
Non-alcoholic steatohepatitis[23,100-103]
Inflammation[100,104-112]
Oxygenation[113]
Elimination
Increased glomerular filtration rate[114,115]
Genetic factors
Pharmacodynamics
Genetic factors[116-119]
Endocrine factors[120-126]
Psychological factors[127]
Nociception[128-132]

2.3 Hepatic Drug Metabolism in Obese Subjects

Among liver diseases, non-alcoholic steatohepatitis is frequently reported in obesity and may progress to cirrhosis and end-stage liver disease.[145] The inflammatory infiltrate and cytokine expression play a role in the development of fibrogenesis.[146,147] Different stages of non-alcoholic steatohepatitis may influence morphine pharmacokinetics.[100-102] In human percutaneous biopsy samples, a decrease in UGT messenger RNA (mRNA) levels, which correlated with inflammation scores, was observed in patients with various forms of acute liver disease.[100-102] However, despite contradictory results, it was generally accepted that glucuronidation capacity is unaffected by most liver disease, especially steatohepatitis. However, during end-stage liver disease, patients with a portal shunt are at risk of drug toxicity because the shunt diverts much of the blood away from the liver and therefore away from most metabolizing enzymes. Hasselström et al.[23] found significantly lower plasma clearance, a longer $t_{½}$ and higher oral

bioavailability of morphine in seven patients with cirrhosis than in patients with normal hepatic function.

Glucuronidation is the main metabolic pathway of morphine. Factors affecting glucuronidation include cigarette smoking, age, sex and obesity.[103] Glucuronidation has been shown to be increased in obese subjects but no specific information is available on UGT2B7, which metabolizes morphine. Likewise, whether steatohepatitis has a specific effect on UGT2B7, P-gp and/or MRP2 or MRP3 is currently unknown. Morphine has a high total plasma clearance (21.1 ± 3.4 mL/min/kg) mainly due to UGT2B7-mediated metabolism, which classifies morphine as a high-extraction drug.[23] Thus changes in hepatic blood flow occurring in obese subjects may increase its hepatic plasma clearance.

In addition, for the drug-metabolizing enzymes to function normally, a sufficient supply of oxygen and nutrients is necessary. Changes in oxygen delivery due to pulmonary or cardiovascular disease may alter metabolism.[113] In the case of chemotherapeutic agents, susceptibility to drugs is greatly affected by hypoxia, which enhances resistance to these agents.[148] Collectively, hepatic, inflammatory and pulmonary consequences of obesity (apnoea syndrome and Pickwick syndrome) may thus alter drug metabolism and morphine pharmacokinetics.

2.4 Distribution and Renal Elimination in Obese Subjects

Dosage modifications in obesity are driven by routine determination of drug concentrations in plasma. Drug distribution into tissue is affected by body composition, regional blood flow and physico-chemical properties of the drug such as lipophilicity and plasma protein binding. Body composition is dramatically different in obese versus non-obese subjects. The increased adipose tissue and lean body mass characterizing obesity is associated with high cardiac output, increased blood volume and an increased glomerular filtration rate.[91-94,98,99,114,115,145,149] In non-obese subjects, approximately 65% of total body water is intracellular versus only 35% in the extracellular compartment. An increase in total body water, with expansion of the extracellular compartment relative to the intracellular compartment, is observed in obese patients.[91,95,96] Waki et al.[97] reported an increase in total body water by 12.9 litres in obese compared with normal-weight women. Moreover, hydration of the fat-free mass appears to be significantly higher in obese versus non-obese subjects.[92] Extracellular water, hydration of the fat-free mass and adipose tissue may influence the V_d of drugs. Various studies have described the differences between obese and non-obese subjects in drug pharmacokinetics. We report some of them in table IV.[150-160] The differences in morphine pharmacokinetics in obese versus non-obese subjects has never been reported.

Previous studies have focused on antimicrobial and anaesthetic drugs.[161,162] Hydrophilic drugs generally have a low or moderate affinity for adipose tissue and hence exhibit no increase or a moderate increase in their V_d, which in obesity and in the case of some drugs correlate with an increase in lean body mass; adjustment of aminoglycoside and ciprofloxacin dosage should therefore be based on adjusted body weight (including IBW +40% of excess weight).[155,163-166] However, total bodyweight was a better predictor of the V_d in the case of vancomycin, and a double dose of cefazolin was found to be more effective than a single dose in decreasing postoperative infections in obese patients.[154,167,168]

In the case of lipophilic drugs, including benzodiazepine and opioids, a larger V_d is usually observed in obese versus non-obese patients, and correlates with the degree of obesity. For example, Abernethy and Greenblatt[133] reported a V_d of 158 L in obese subjects and 63 L in lean subjects after administration of a 15 mg chlorazepate capsule, and the value of the V_d remained greater after correction for bodyweight. But in the case of thiopental sodium and remifentanil, the V_d was more closely related to lean body mass and cardiac output than to total body water.[88,151,169-174] The estimates of the distribution volumes for remifentanil (mean central volumes of distribution of 7.5 L and 6.8 L in the obese and lean groups, respectively, and mean peripheral compartment volumes of distribution of 8.7 L and 7.6 L in the obese and lean groups, respectively) are somewhat less than expected for lipid-soluble molecules and revealed only modest distribution into body tissues.[173] Morphine has an intermediate V_d in humans (ranging from 0.95 to 3.75 L/kg), probably related to its lipophilicity.[26] The question of the role of adipose tissue on morphine tissue distribution, which in turn may affect its pharmacokinetics, has not been investigated.

Obesity affects the glomerular filtration rate, which may alter clearance of antibacterials that are eliminated unchanged through the kidney.[175] Obese kidney donors have a larger glomerular planar surface area than non-obese donors, thus confirming the concept that a higher BMI is associated with larger glomeruli in humans.[114,115] Therefore, in the case of hydrophilic drugs, obese patients may require more frequent drug administration.[155,163-166]

A prolonged $t_{½}$ is observed with lipophilic drugs.[133,150,162,174] For example, diazepam $t_{½}$ was greatly prolonged in obese subjects (82 vs 32 hours in non-obese subjects), with no change in total metabolic clearance.[133] Differences in drug

Table IV. Examples of drug pharmacokinetics in obese and non-obese subjects[a]

Drug dosage and subjects	$t_{½}$ (h)		V_d		CL		Reference
	obese	control	obese	control	obese	control	
Examples of drugs used in anaesthesiology							
Sufentanil 4 μg/kg: single IV bolus; 8 obese and 8 control	3.5 (1.4)*	2.25 (0.7)	9 (2.8) L/kg IBW*	5 (1.7) L/kg IBW	32.9 (12.5) L/kg IBW	26.4 (5.7) L/kg IBW	150
Midazolam 2.5–5 mg IV bolus; 20 obese and 20 control	8.4 (0.84)*	2.7 (0.34)	311 (27) L = 2.7 L/kg TBW*	114 (7) L = 1.7 L/kg TBW	472 (0.38) mL/min*	530 (34) mL/min	151
Vecuronium 0.1 mg/kg IV bolus; 7 obese and 7 control	2 (0.7)	2.21 (0.9)	0.8 (0.3) mL/kg IBW	0.9 (0.3) mL/kg IBW	4.65 (0.89) mL/min/kg IBW	5.02 (1.13) mL/min/kg IBW	152
Examples of anti-infectives drugs							
Daptomycin 4 mg/kg TBW IV infusion; 6 obese and 6 control	8.12 (21)	8.04 (29)	V_z: 0.18 (18.1) L/kg IBW* = 0.09 (12.9) L/kg TBW*	V_z: 0.12 (14.0) L/kg IBW = 0.11 (11.9) L/kg TBW	0.27 (0.45) mL/min/kg IBW = 0.13 (0.33) mL/min/kg TBW*	0.18 (0.53) mL/min/kg IBW = 0.17 (5.1) mL/min/kg TBW	153
Vancomycin 1 g IV over 40 min; 6 obese and 4 control	3.2*	4.7	43.0 L = 0.26 L/kg TBW*	28.9 L = 0.39 L/kg TBW	187.5 mL/min*	80.8 mL/min	154
Ciprofloxacin single 400 mg IV dose over 1 h; 17 obese men and 11 control	4.26 (0.66)	4.0 (0.34)	V_{ss}: 269.17 (51.64) L* V_{ss}/kg: 2.46 (0.42) L/kg	V_{ss}: 219.03 (35.80) L V_{ss}/kg: 3.06 (0.31) L/kg	897.44 (159.57) mL/min*	744.44 (120.51) mL/min	155
Others							
Paracetamol (acetaminophen) single 650 mg IV dose; 21 morbidly obese and 21 control	OM: 2.55 OW: 2.32	CM: 2.76 CW: 2.66	OM: 108.5 L* = 0.81 L/kg TBW* OW: 61.4 L* = 0.71 L/kg TBW*	CM: 77.0 L = 1.09 L/kg TBW CW: 51.6 L = 0.95 L/kg TBW	OM: 484 mL/min* OW: 312 mL/min* No difference between groups after correction for TBW	CM: 323 mL/min CW: 227 mL/min	156

Continued next page

Table IV. Contd

Drug dosage and subjects	$t_{½}$ (h)		V_d		CL		Reference
	obese	control	obese	control	obese	control	
Cyclophosphamide 7 overweight and 5 obese	8.5	4.8	37.1 L	34.5 L	60.6 mL/min	91.3 mL/min	157
Isofosfamide 4 obese and 12 control	6.4*	4.9	42.8 L*= 0.55 L/Kg TBW	33.7 L = 0.53 L/Kg TBW	76.0 mL/min	72.2 mL/min	158
Lithium (oral lithium citrate) 31.4 mEq; 10 obese and 8 control	18.7 (4.0)*	25.6 (9.6)	0.42 (0.1) L/Kg TBW*	0.66 (0.15) L/Kg TBW	33.9 (7.0) mL/min*	23.0 (6.2) mL/min	159
Glipizide 5 mg single dose 12 obese and 8 control	5.0 (2.3)	5.2 (2.0)	V_d/F: 17.2 (4.3) L	V_d/F: 19.5 (4.4) L	CL/F: 0.18 (0.06) mL/min	CL/F: 0.12 (0.06) mL/min	160

a Values are expressed as mean (SD).

CL = apparent total body clearance; **CL/F** = apparent oral clearance; **CM** = control men; **CW** = control women; **IBW** = ideal bodyweight; **IV** = intravenous; **OM** = obese men; **OW** = obese women; $t_{½}$ = terminal elimination half-life; **TBW** = total bodyweight; V_d = apparent volume of distribution; V_d/F = volume of distribution after oral administration; V_{ss} = steady-state volume of distribution; V_z = apparent volume of distribution during the terminal phase; * $p < 0.05$ vs control.

lipophilicity in morbidly obese populations may also explain differences in postoperative recovery after anaesthesia with desflurane versus sevoflurane.[176]

Morphine has relatively low renal clearance compared with its total plasma clearance, suggesting that modification of glomerular filtration occurring in obese subjects may only weakly affect its total clearance. However, M6G and M3G are mainly eliminated by renal clearance and the higher glomerular filtration in obese subjects may increase renal clearance of M6G and M3G, leading to decreased M6G pharmacological activity.

The pharmacokinetics of drugs are, in general, affected to various degrees by obesity, and the extent of this effect is difficult to predict.[161] The situations thus created illustrate the differences between drug distribution in obese versus non-obese subjects, as well as the need for predictive markers that could be used routinely to individualize drug dosage.

2.5 Inflammation and Drug Metabolism

Obesity is a state of chronic low-grade inflammation.[146,177-179] Adipose tissue is considered as a secretory organ that produces adipokines (leptin and adiponectin) and other cytokines such as interleukin (IL)-6, tumour necrosis factor (TNF)-α and vascular endothelial growth factor.[179,180] It has been suggested that inflammation and infection may increase drug bioavailability.[100,104-112] Inflammatory agents increase the production of interferon, TNF and mainly IL-1 and IL-6.[181] TNF and IL-1 induce the production of IL-6, which inhibits drug metabolism *in vitro*. A recent study conducted in six bone marrow transplant recipients showed that the peak serum concentration of IL-6 after transplantation was systematically followed by an increase in ciclosporin serum concentrations.[182]

Liver and intestinal P-gp and UGT2B7 are the two major proteins involved in the intestinal and hepatic first-pass of morphine in humans. One study revealed a trend towards downregulation of most UGTs in the mouse liver during acute inflammation.[104] A decrease in UGT mRNA levels that correlated with inflammation scores has been observed in human tissue samples from percutaneous liver biopsies.[100] In addition, expression and activity of P-gp were decreased by IL-6, IL-1, IL-10 and TNF *in vitro* and in animal studies during inflammation in the CNS and intestinal tract.[105-110] Hartmann et al.[106] also reported a 40–70% reduction in the expression and mRNA levels of P-gp in the livers of IL-6-treated mice. Buyse et al.[109] reported an increase in P-gp expression in the non-inflamed intestine of rats with colitis, which may reflect the existence of an adaptative mechanism to compensate for a loss

of P-gp functionality. A study of the long-term consequences of continuous exposure of rat brain capillaries to low levels of TNFα and endothelin-1 showed a rapid decrease in P-gp transport activity followed by an increase in this activity and P-gp protein expression.[111] In humans, Fakhoury et al.[112] compared P-gp mRNA and protein levels and functionality in 19 non-inflamed duodenal biopsies from children with Crohn's disease with control duodenum, and found higher P-gp levels in the children with Crohn's disease, although the disease was silent at the time of the study.

MRP2 (another transporter involved in the biliary, intestinal and renal transport of morphine and its glucuronidated metabolites) mRNA levels were also lower during sepsis or hepatitis C infection, and cytokines (IL-1β, TNFα, IL-6) may be involved in reducing the expression level of MRP2, as shown in animals and *in vitro*.[17] To date, transporter activity has not been specifically studied in obesity, although this clinical setting may reflect chronic inflammation and alter morphine pharmacokinetics and pharmacodynamics due to alteration in morphine metabolism transport.

2.6 Nociception, the μ Opioid Receptor and Obesity

The most frequent type of pain in obesity is joint pain, mainly due to osteoarthritis.[183] It remains unclear whether or not differences in pain perception exist between obese and non-obese patients and influence morphine requirements. Many factors may influence nociception, including pain mechanisms (mechanical factors and possibly inflammation in the case of obesity), smoking, alcohol (ethanol) consumption, pathological conditions, psychological and genetic factors.[127,184]

Few studies have reported contradictory results regarding nociception in obese populations and differences in the methods of assessment used may account for the mixed findings. In humans, Pradalier et al.,[128] using a nociceptive flexion reflex (the sapheno-bicipital reflex), reported increased pain, with a significantly lower threshold in obese patients than in non-obese patients. McKendall and Haier[129] also found lower mechanical pain thresholds in obese subjects, as assessed by a constant force applied to the finger. Conversely, in a sample of 206 healthy subjects, Khimich,[130] who used a method based on dosage pressure by a needle on the forearm, found that obese patients had a higher pain sensitivity threshold and then felt less pain. Zahorska-Markiewicz et al.,[131] using transcutaneous electrical stimulation, found an elevated pain threshold in obese subjects. However, Raymond et al.[132] detected a significantly higher pain threshold in obese subjects with binge-eating disorder than in those without binge-eating disorder but the BMI and pain threshold were not correlated, suggesting abnormal physiological painful stimuli in patients with binge-eating disorder.

Interestingly, a recent study in parturient women showed that obese patients required smaller amounts of intrathecally administered analgesics than lean patients. Several factors might account for this, including polymorphisms of the μ opioid receptor, reduced analgesic efflux or the anatomy of the CNS, characterized by increased intrathecal pressure in obesity.[185]

Moreover, common circuits are involved in food behaviour and in nociception, which may explain differences in nociception and the responses to morphine analgesia in obese patients: endogenous opioid, central melanocortine and dopamine systems.[120-126] Interestingly, a mutation was recently identified in a subject with severe obesity, impaired learning and memory, who also had impaired nociception, illustrating the possibility that genetic factors may predispose to both obesity and impaired nociception.[186-188] Pain perception, the efficacy of morphine and its adverse effects, the responses to addictive opioid drugs, the rewarding properties of opioid compounds and the responses to stress mediated by the hypothalamic pituitary adrenal axis, are all controlled by the μ opioid receptor. Different genotypes of this receptor may modify these different responses.[189,190] Recent studies support the possibility that the μ opioid receptor may have a role in behaviour and suggest that in obesity, the opioid system is deregulated which, if true, would lead to differences in morphine pharmacodynamics between obese and non-obese patients.[26,191-198]

Since there are associations between the frequency of *OPRM1*, *COMT* and *MDR1* polymorphisms and morphine efficacy and tolerance, as well as vulnerability to dependence on addictive substances, and because similarities between obesity and addictions have been reported, the prevalence of the aforementioned genetic polymorphisms may be clinically relevant variables to study in obese versus non-obese patients.[199] Some studies have recently reported a relation of some polymorphism of these genes and obesity or weight gain. A stronger influence of the *MDR1* (G2677T and C3435T) polymorphisms on risperidone-induced weight gain has been recently reported among 108 female schizophrenic patients.[116] Among 5448 Japanese individuals, the G2677T polymorphism was also significantly associated ($p = 0.0003$) with obesity.[117]

Xu et al.[118] recently reported that tagging SNPs (tSNPs) in the *OPRM1* gene (rs1799971 in exon 1, and rs514980 and rs7773995 in intron 1) were significantly associated with the BMI in a Uyghur population. Recently, Davis et al.[200] reported a significative difference in the prevalence of the G allele between the population of obese patients with binge eating

(allele G = 0.18; mean BMI = 35.6 kg/m^2) and the population of obese patients without binge eating (allele G = 0.10; mean BMI = 39.2 kg/m^2), suggesting that binge eating is a genetically determined subtype of obesity. It has also been suggested that *COMT* polymorphism may play a role in the risk of obesity following antipsychotic drug usage and in the general population. In a cohort of 240 Swedish men, homozygous subjects for the low-activity allele (met) displayed higher blood pressure, heart rates, waist-to-hip ratios and abdominal sagittal diameters as compared with heterozygous subjects.[119]

3. Conclusions and Perspectives

This review has not been designed to present all current aspects of opioid pharmacology but rather to highlight the lack of pharmacokinetic and pharmacodynamic data on morphine in obese subjects and to focus on some selected findings that may be clinically relevant to the morbidly obese population. Obesity resulting from environmental and genetic factors is associated with changes in body composition, endocrine signals, inflammatory status and morbidity. These changes may affect drug disposition and may partly explain interindividual variations in morphine efficacy and toxicity. We think that all theses parameters merit investigation. Studying morphine pharmacokinetics and pharmacodynamics in obese patients and incorporating the currently known morphine pharmacogenomic aspects would provide very useful clinical information on issues such as nociception and the influence of body composition, inflammation and concomitant medications on morphine pharmacokinetics and analgesia. Several issues such as the initial dosages in obesity and gastric bypass or the consequences of drug-drug interactions are still unresolved.

Further studies are therefore needed to determine the influence of P-gp, UGT2B7, MRP2, COMT and OPRM1 on oral morphine disposition and the dose-effect relationship in obesity. In addition, pharmacological studies before and after bariatric surgery may highlight the role of the intestinal barrier in the disposition and clinical efficacy of morphine. A better understanding of the sources of pharmacokinetic variability may improve the use of opioids in the clinical management of obese patients, especially in morbidly obese subjects undergoing bariatric surgery.

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