REVIEW

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Influences of Obesity and Bariatric Surgery on the Clinical and Pharmacologic Profile of Rivaroxaban

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ABSTRACT

The health implications of obesity are myriad and multifaceted. Physiologic changes associated with obesity can affect the absorption, distribution, metabolism, and excretion of administered drugs, thereby altering their pharmacologic profiles. In 2016, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis published recommendations about the use of direct oral anticoagulants (DOACs) in obese patients. This guidance provides uniform recommendations for all DOACs, yet data suggest that individual agents may be affected to different degrees by obesity. Moreover, there are no recommendations currently available to guide DOAC use in bariatric surgery patients, in whom anatomic and physiologic changes to the digestive system can influence drug pharmacokinetics. Our review of the available literature indicates that the clinical profile of the DOAC rivaroxaban is not affected by high weight or bariatric surgery; hence, it does not appear that rivaroxaban dosing needs to be altered in these patient populations.

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An estimated 13% of the world's population is currently obese (body mass index [BMI] $\geq$30 kg/m^2), and the incidence is increasing along with the associated health and economic burden.[1] Obesity has multifaceted impacts on approaches to patient health and disease management, including selection of anticoagulant therapy. Considered a prothrombotic and proinflammatory state,[2] obesity is a risk factor for conditions where anticoagulant therapy is indicated (eg, hip/knee replacement,[3] atrial fibrillation,[4] venous thromboembolism[5]). Beyond inducing a prothrombotic state, obesity may influence thrombotic risk through its effects on the clinical pharmacology (pharmacokinetics/pharmacodynamics) of anticoagulants, potentially leading to either undercoagulation or overcoagulation, thereby increasing the risk for thrombotic or bleeding events.

Best practices about the use of anticoagulants in obese patients remain to be determined. The emergence of direct oral anticoagulants (DOACs) broadens the anticoagulant treatment armamentarium, but DOAC use in morbidly obese patients (BMI $\geq$40 kg/m^2) has been called into question. In 2016, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) published guidance statements that included a suggestion to not use DOACs in patients with a BMI $>$40 kg/m^2 or weight $>$120 kg due to limited clinical data and concerns about the potential effects of weight extremes on the pharmacology of these agents.[6] If DOACs are used in these patients, the ISTH guidance suggests monitoring drug-specific peak and trough levels. The ISTH recommendations apply to all DOACs, although evidence suggests that their clinical and pharmacologic profiles may not be influenced to the same extent by weight.[7]

One consequence of the obesity epidemic is the rapidly growing use of bariatric surgery. Bariatric surgery, which involves restricting the functional size of the stomach or

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inducing nutrient malabsorption, has shown favorable results for reducing weight and can produce improvements in obesity-related comorbidities.[8,9] From a drug-delivery standpoint, a history of bariatric surgery is worth consideration because the accompanying anatomic and physiologic changes[10] may affect drug pharmacokinetics, thereby potentially influencing efficacy and safety.[8,9] Understanding changes in response to anticoagulant therapy after bariatric surgery is essential due to the elevated thrombotic risk in this patient population.[11] Little is known, however, about the pharmacology of DOACs after bariatric surgery, both in the immediate postoperative period and during long-term therapy.

Rivaroxaban is a DOAC that has been extensively studied in a variety of clinical indications, including those with a high likelihood of comorbid obesity. Rivaroxaban has also been studied in a small number of healthy subjects both prior to and following bariatric surgery. The purpose of this review is to assess the available evidence for use of rivaroxaban in the context of obesity or bariatric surgery by examining the published literature for studies that have evaluated the clinical or pharmacologic profile of rivaroxaban in these patient populations.

CLINICAL SIGNIFICANCE

- Recent International Society on Thrombosis and Haemostasis guidelines questioned the use of direct oral anticoagulants (DOACs) in obese patients. The recommendation was uniform for the DOAC drug class.
- Moreover, there are currently no recommendations about DOAC usage in patients who have undergone bariatric surgery.
- This review assessed the available evidence for rivaroxaban, and data retrieved indicate that its clinical profile is not affected by high body weight or bariatric surgery; hence, no dose adjustment is needed.

METHODS

Articles for inclusion in this review were identified from the published literature by interrogation of the MEDLINE database and by search of abstracts from relevant scientific congresses. Search terms included pharmacokinetics, pharmacodynamics, obese, obesity, overweight, body weight, BMI, bariatric surgery, and gastric bypass in conjunction with rivaroxaban/BAY 59-7939. In addition, reference lists from included publications were used to identify other articles of interest. All publications pertinent to the subject matter were included in the manuscript; no exclusions based on study criteria or date of publication were applied.

RIVAROXABAN AND OBESITY

The extent of drug exposure is dependent on its absorption, distribution, metabolism, and excretion. There is evidence to suggest that each of these components may be influenced by obesity.[9] However, whether or not drug exposure is affected to a measurable or clinically meaningful degree is agent specific. In the case of rivaroxaban, pivotal clinical trials, clinical pharmacology studies, and population models provide insights into the impact of obesity on drug exposure.

Pharmacokinetic/Pharmacodynamic Studies

A clinical pharmacology study was conducted to assess the influence of weight extremes on the general safety and pharmacologic profile of rivaroxaban after a single 10-mg oral dose.[12] The study enrolled 48 healthy subjects and compared results in subjects in weight categories of ≤50 kg (low weight), 70-80 kg (normal weight), and >120 kg (high weight). No differences in safety were observed among weight groups. The pharmacokinetic profile of rivaroxaban was comparable in subjects in the normal- and high-weight groups (**Figure 1**),[12] and the time course of factor Xa activity inhibition by rivaroxaban was largely unaffected by weight (**Figure 2**).[12] The authors concluded that the overall limited influence of weight on the pharmacologic profile of rivaroxaban (ie, generally <15% change compared with normal weight) makes it unlikely that dose adjustment is necessary for patients with weight extremes. This study formed the basis for the current rivaroxaban prescribing information, which does not suggest dose adjustment based on weight.[13]

Insights into the influence of weight on the pharmacology of rivaroxaban in more diverse patient populations have been obtained through population modeling conducted using data from multiple clinical trials in various indications. Two publications have reported on the

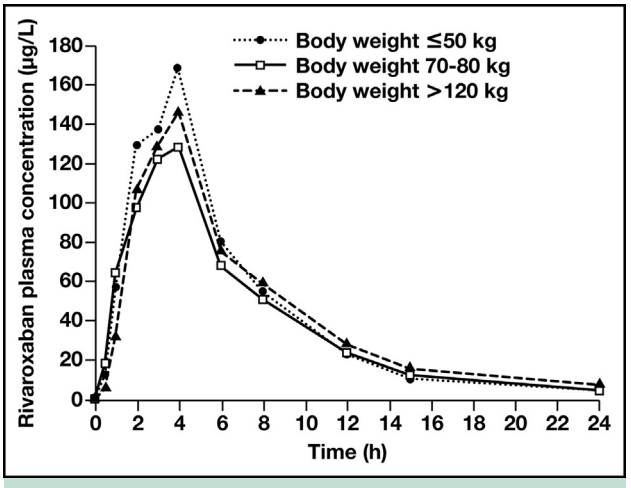

Figure 1 Mean rivaroxaban plasma concentration-time curve after administration of a single 10-mg oral dose. Each weight group included 12 healthy subjects. Reprinted from Kubitza et al (2007).[12]