论著·临床医学

*CYP3A4/5*基因型相同患者中正常体质量与超重状态对舒芬太尼代谢影响的前瞻性临床研究

刘冠磊[1],蒋 颖[1],杨 波[2],秦志刚[1,3],冯力元[3],薛正威[1],邱 芳[1],陈春梅[1],邹文忠[1],李 鹏[3],顾健腾[1] 陆军军医大学(第三军医大学)第一附属医院:[1]麻醉科,[2]药学部;[3]陆军军医大学(第三军医大学)药学与检验医学系生药学与中药学教研室,重庆

[**摘要**] **目的** 探索体质量指数(body mass index,BMI)为正常、超重与*CYP3A4/5*酶基因型人群的舒芬太尼药代动力学特征。**方法** 招募2020年11月至2021年9月就诊于陆军军医大学第一附属医院并在全身麻醉下行腔镜手术的患者,术前采集全麻腔镜手术患者口腔拭子,使用人CYP3A4/5基因试剂盒行基因分型,依其多态性组合对舒芬太尼代谢潜在影响程度及CYP3A4/5酶不同基因型组合的人群占比,将患者分为Ⅰ(3A4纯合突变或3A4杂合突变+3A5纯合突变)、Ⅱ(3A4杂合突变+3A5杂合突变)、Ⅲ(3A4野生型或3A4杂合突变+3A5野生型)类人群,并根据正常体质量组(BMI >18.5~24.0 kg/m^2)、超重组(BMI 24~<28 kg/m^2)分为2组进行药物代谢参数的统计学分析。常规全麻诱导(舒芬太尼0.5 μg/kg)后采集静脉血样,高效液相色谱-质谱联用(high performance liquid chromatography-mass spectrometry,HPLC-MS)检测舒芬太尼血药浓度变化。分别计算3类人群中正常体质量组和超重组及不同基因型组合分组条件下舒芬太尼的药代数据,并进行统计学分析。**结果** 入组的90名受试者完成血药浓度检测,8例患者血液样本受到污染(含1例麻醉时间不足2 h),3例属低体质量或超重人群,最终79名纳入正常体质量组和超重组的药代分析。与正常体质量组相比,超重组中央室分布容积显著减少(P<0.05),外周室分布容积、总清除率、外周室清除率、分布半衰期、清除半衰期、血药浓度-时间曲线下面积等无显著差异。Ⅰ类人群(n=26)中,超重患者(n=13)与正常体质量患者(n=13)相比,中央室分布容积、周边室分布容积和周边室清除率显著减少(P<0.05),其余药代参数无显著差异;Ⅱ(n=25)和Ⅲ(n=28)类人群中的超重患者与正常体质量患者相比,各药代参数无显著差异。**结论** 在CYP3A4/5突变程度基因型组合相同的人群中,超重和正常体质量患者舒芬太尼代谢无差异;Ⅰ类人群中超重患者舒芬太尼的外周室分布范围更小,且代谢过程显著减弱。

[**关键词**] 舒芬太尼;药物代谢动力学;BMI;CYP3A酶;个体化用药

[**中图法分类号**] R614.2;R969.1 [**文献标志码**] A

Effects of normal body weight and overweight status on metabolism of sufentanil in patients with same *CYP3A4/5* genotype: A prospective clinical study

LIU Guanlei[1], JIANG Ying[1], YANG Bo[2], QIN Zhigang[1,3], FENG Liyuan[3], XUE Zhengwei[1], QIU Fang[1], CHEN Chunmei[1], ZOU Wenzhong[1], LI Peng[3], GU Jianteng[1]

[1]Department of Anesthesiology, [2]Department of Pharmacy, First Affiliated Hospital, Army Medical University (Third Military Medical University), Chongqing; [3]Department of Pharmacognosy and Traditional Chinese Pharmacy, Faculty of Pharmacy and Laboratory Medicine, Army Medical University (Third Military Medical University), Chongqing, China

[**Abstract**] **Objective** To explore the pharmacokinetic characteristics of sufentanil in individuals

[**基金项目**] 重庆英才项目基金(CQYC20220303588);重庆市科卫联合医学科研重点项目(2026ZDXM002)

[**通信作者**] 顾健腾,E-mail:jiantenggu@tmmu.edu.cn

2097-0927/Copyright © 2025,陆军军医大学(第三军医大学)。这篇开放获取文章遵循CC BY许可协议(https://creativecommons.org/licenses/by/4.0/)

引用格式:刘冠磊,蒋颖,杨波,等. CYP3A4/5基因型相同患者中正常体质量与超重状态对舒芬太尼代谢影响的前瞻性临床研究[J]. 陆军军医大学学报,2025,47(22):2774-2782. DOI:10.16016/j.2097-0927.202509006.

Citation:LIU G L,JIANG Y,YANG B,*et al*. Effects of normal body weight and overweight status on metabolism of sufentanil in patients with same CYP3A4/5 genotype: A prospective clinical study[J]. J Army Med Univ,2025,47(22):2774-2782. DOI:10.16016/j.2097-0927.202509006.

with normal body mass index (BMI), overweight BMI, and different *CYP3A4/5* enzyme genotypes. **Methods** The patients receiving laparoscopic surgery under general anesthesia in the First Affiliated Hospital of Army Medical University from November 2020 to September 2021 were prospectively recruited in this study. Before the operation, the oral swabs were collected from all the patients for genotyping using the human CYP3A4/5 gene kit. Based on the potential impact of combination of their polymorphisms on sufentanil metabolism and the proportion of different genotype combinations of CYP3A4/5 enzymes, the patients were divided into groups I (3A4 homozygous mutation or 3A4 heterozygous mutation+3A5 homozygous mutation), II (3A4 heterozygous mutation + 3A5 heterozygous mutation), and III (3A4 wild type or 3A4 heterozygous mutation + 3A5 wild type). According to their BMI, they were also assigned into a normal body weight group (18.5~24.0 kg/m^2) and an overweight group (24~ <28 kg/m^2), and the differences in drug metabolism parameters were statistically analyze between the 2 groups. After routine general anesthesia induction (sufentanil 0.5 μg/kg), venous blood samples were collected to detect the changes in its concentration using high performance liquid chromatography-mass spectrometry (HPLC-MS). The pharmacokinetic data of sufentanil were calculated between the normal BMI group and overweight group in all participants and between the 2 body weight groups among those with different genotype combinations. **Results** Among the 90 participants completing the blood drug concentration test, 8 patients had their blood samples contaminated (including 1 case with an anesthesia duration of <2 h), and 3 were excluded due to low weight or overweight. Eventually, 79 participants were included in the pharmacokinetic analysis on the normal body weight group and the overweight group. Compared with the normal body weight group, the central compartment volume of distribution in the overweight group was significantly reduced (P<0.05), while no obvious differences were observed between the 2 groups in terms of peripheral compartment volume of distribution, total clearance rate, peripheral compartment clearance rate, distribution half-life, clearance half-life, and area under the blood concentration-time curve. In group Ⅰ (n=26), the overweight patients (n=13) had significantly reduced central compartment volume of distribution, peripheral compartment volume of distribution, and peripheral compartment clearance rate when compared with the normal body weight patients (n=13) (P<0.05), while no differences were observed in other pharmacokinetic parameters. In groups Ⅱ (n=25) and Ⅲ (n=28), the overweight patients and normal body weight patients had no statistical differences in all pharmacokinetic parameters. **Conclusion** Among the patients with the same genotype combination of CYP3A4/5 mutations, there was no difference in the metabolism of sufentanil between the overweight and normal weight patients. Additionally, in the population of 3A4 homozygous mutation or 3A4 heterozygous mutation+3A5 homozygous mutation, the overweight patients have smaller peripheral distribution range of sufentanil, and weakened metabolic process.

[**Key words**] sufentanil; pharmacokinetics; body mass index; CYP3A enzyme; individualized medication

Supported by the Fund of Chongqing Talent Program (CQYC20220303588), and the Chongqing Key Joint Medical Research Project (2026ZDXM002).
Corresponding author: GU Jianteng, E-mail: jiantenggu@tmmu.edu.cn

舒芬太尼是目前临床上最常用的高选择性μ-阿片受体激动剂类镇痛药,其可能引发头晕、恶心、呕吐、呼吸抑制等副作用,这些不良反应可能导致患者出现严重后果甚至死亡[1-3]。随着加速康复外科(enhanced recovery after surgery, ERAS)理念的持续深化与优化,临床治疗策略正逐步转向减少阿片类药物相关不良反应(如术后胃肠功能抑制、恶心呕吐及平衡障碍等),以促进患者术后早期活动[4]。在此背景下,实施个体化精准镇痛方案已成为当前围术期管理的重点方向。舒芬太尼在体内主要由肝脏中的细胞色素P450 3A(cytochrome P450 3A, CYP3A)酶类代谢[5],CYP3A4/5亚型是肝脏CYP450酶的主要组成部分,占肝脏CYP450 3A总量的30%~60%。研究表明,CYP3A4的活性差异约有20%可归因于体质量指数

(body mass index,BMI)、饮酒及吸烟等外源性因素[6]。BMI增高可导致肝脏内CYP3A4活性降低,从而使得药物的清除率降低[7]。然而,目前关于CYP3A5酶在药物代谢中的作用机制研究还少有文献报道。

近年公共卫生领域的流行病学研究调查显示,我国BMI超重(BMI 24~<28 kg/m^2)与肥胖(BMI ≥28 kg/m^2)的患病率呈逐年上升[8],超重、肥胖患者的外科手术量也有所增加[9]。超重增加了许多疾病的发病率[10],此类人群往往易发展为肥胖症,已经成为我国又一大致死致残的危险因素[11],是我国面临的重大公共卫生问题。此类患者往往合并多系统疾病,如高血压、糖尿病、高脂血症等[12]。临床中最常用的给药依据指标是总体质量(total body weight,TBW),它与正常体质量患者的药物代谢动力学(pharmacokinetics,PK)参数(如清除率和表观分布容积)相关性良好,但在超重患者尤其是肥胖患者中相关性不足[13]。超重的特征表现为机体脂肪组织质量所占总体质量比例显著升高[14],该生理差异可引起药物分布容积改变。因此,当采用基于TBW的传统给药方案时,亲脂类药物在组织中的异常蓄积可能导致PK参数异常,继而增加治疗相关毒性的临床风险[13]。在中国CYP3A4/5不同突变程度基因型组合人群中,缺乏正常体质量和超重人群舒芬太尼的药物代谢能力是否存在差异的研究,既往的药物代谢研究将人群分为肥胖和非肥胖人群,忽略了超重与正常体质量之间的生理差异可能会引起药物代谢能力不同,依据BMI精准化用药不够完善。因此,本研究拟基于CYP3A4/5酶突变程度分类,分析正常体质量人群与超重人群对舒芬太尼药代动力学的影响,为临床麻醉中舒芬太尼的剂量使用提供参考依据。

1 资料与方法

1.1 试验对象及分组

本研究在课题组前期分析*CYP3A4/5*基因多态性对舒芬太尼PK参数影响及性别因素对CYP3A4/5酶活性调控作用的基础上[15],进一步基于受试者BMI水平进行分层分析,前期研究结果发现不同突变程度的CYP3A4/5基因型组合可显著改变舒芬太尼的药物代谢能力,且性别是影响药物代谢的重要因素。研究招募2020年11月至2021年9月就诊于陆军军医大学第一附属医院,并在全身麻醉下行腔镜手术的患者,签署知情同意书后,术前进行*CYP3A4*、*CYP3A5*无创基因检测而后分层随机抽样入组。本研究通过陆军军医大学第一附属医院伦理委员会批准[KY2020124和(A)KY2021037],同时在中国临床试验注册中心完成注册(ChiCTR2000037436)。纳入标准:①年龄18~59岁;②BMI 18~28 kg/m^2;③ASA Ⅰ-Ⅲ级;④Child A级;⑤拟全麻下行腔镜手术(胃肠、泌尿、食管、肺脏、神经)且时长>120 min。排除标准:①合并严重心、脑、血管、呼吸系统疾病、糖尿病或严重肝肾功能不全;②术前合并有慢性疼痛综合征、精神障碍性疾病或中枢神经系统器质性疾病、有效循环血容量不足(中心静脉压<5 cmH_2O)或持续性低血压(平均动脉压<65 mmHg);③既往有阿片类药物过敏史、药物滥用史、长期酗酒(酒精摄入量≥40 g/d)、吸毒史或长期服用镇痛药物者;④麻醉前7 d内摄入可诱导或抑制CYP3A酶表达的食物或药物、麻醉前14 d内使用单胺氧化酶抑制剂等可能干扰舒芬太尼代谢者;⑤妊娠期、哺乳期女性。

依据CYP3A4/5酶多态性组合对舒芬太尼代谢潜在影响程度即CYP3A4/5酶基因突变携带人群药物代谢能力减弱及CYP3A4/5酶不同基因型组合的人群占比(即Ⅰ类人群占比10.72%、Ⅱ类人群占比29.08%、Ⅲ类人群占比60.2%),将患者分为Ⅰ(3A4纯合突变或3A4杂合突变+3A5纯合突变,赋4~6分)、Ⅱ(3A4杂合突变+3A5杂合突变,赋3分)、Ⅲ(3A4野生型或3A4杂合突变+3A5野生型,赋0~2分)类人群,具体分组情况见表1[15]。根据入组的255例受试者基因检测结果,采用随机信封法,三组受试者分别按照1∶1、1∶1、1∶3的概率从Ⅰ、Ⅱ、Ⅲ类人群中抽取且三组受试者中男女比例为1∶1,入组人数为每组30人,共抽取90名受试者参与舒芬太尼药物代谢临床试验。将研究对象按国家卫生健康委员会医政司肥胖症诊疗指南(2024年版)标准分为正常体质量组(BMI>18.5~<24.0 kg/m^2)、超重组(BMI 24~<28 kg/m^2),系统考察正常体质量组和超重组患者对舒芬太尼PK参数的影响,并探讨BMI与*CYP3A4/5*基因型对药物代谢的交互作用。

1.2 试验方案

术前访视时,对符合纳排标准的患者采集3份口腔咽拭子,1份用人类*CYP3A4*、*CYP3A5*基因多态性检测试剂盒(浙江鼎创医疗科技有限公司)快速检测,另2份备份。共筛选255人,基于国内外相似前瞻性药代研究样本量为15~80例,本研究最终确定招募90例患者参与舒芬太尼药物临床试验,以分层随机抽样选取90人开展临床药物代谢研究。麻醉手术阶段,患者禁食水8 h以上,入手术室后行外周静脉、左侧桡动脉及右侧颈内静脉穿刺置管,用于补液和监测,常规监测心电图、体温、脉搏氧饱和度、呼吸末CO_2浓度、气道压及脑电双频谱指数。麻醉诱导为静脉推注咪达唑仑2 mg、

表1 CYP3A4和CYP3A5等位基因人群分布频率及分组情况(%)

Table 1 Population distribution frequency and grouping of CYP3A4 and CYP3A5 alleles (%)

Genetic typing	Wild-type CYP3A4	Heterozygous mutation of CYP3A4	Pure mutation of CYP3A4	Total
Wild-type CYP3A5	0.51	3.06	3.57	7.14
Heterozygous mutation of CYP3A5	7.65	29.08	2.04	38.77
Pure mutation of CYP3A5	48.98	4.85	0.26	54.09
Total	57.14	36.99	5.87	100

顺式阿曲库铵0.15 mg/kg、枸橼酸舒芬太尼0.5 μg/kg、依托咪酯0.2 mg/kg;维持采用静吸复合麻醉,吸入1%七氟烷,靶控输注丙泊酚2~3 μg/(mL·kg)、瑞芬太尼1~3 ng/(mL·kg),间断推注顺式阿曲库铵0.30~0.45 mg/(kg·h),术中机械通气,依生命体征调整用药及血管活性药物以维持平稳。血样采集与处理采用标准化流程:依据舒芬太尼药代动力学特点,在3~5个半衰期后舒芬太尼基本完成消除,120 min覆盖其从分布相进入消除相的关键过程,能获取消除相初期数据,满足单次推注后药物浓度变化规律分析,因此经外周静脉留置针采集舒芬太尼给药前5 min(基线期)及给药后2、5、10、20、30、45、60、90、120 min共10个时间点各3 mL全血,之后立即用4 ℃冰袋保存转运至实验室。血液样本在4 ℃控温离心机中以3 000 r/min离心10 min,无菌分离血浆,每时间点样本等分为2份(1 mL/管),标记后-80 ℃冻存,最终经符合药品生产质量管理规范(Good Manufacturing Practice,GMP)标准的快递公司冷链送至苏州方达生物技术有限公司,用高效液相色谱-质谱联用(high performance liquid chromatography-mass spectrometry,HPLC-MS)法检测血浆药物浓度并分析数据。

1.3 药物代谢参数处理

使用软件Phoenix WinNonlin 8.1软件拟合二房室模型,计算分布相、消除相的药物代谢动力学参数即中央室表观分布容积(the volume of central compartment,V_1)、周边室分布容积(the volume of equilibrating compartment,V_2)、药物总清除率(systemic clearance,CL)、外周室清除率(elimination clearance of peripheral compartment,CL_2)、药物分布半衰期(distribution half-life,$t_{1/2\alpha}$)、消除半衰期(elimination half-life,$t_{1/2\beta}$)、血药浓度-时间曲线下总面积(total area under the plasma concentration-time curve,AUC_{0-t})、0-∞时的血药浓度-时间曲线下面积(area under the plasma concentration time curve from zero to infinity,$AUC_{0-\infty}$)。

1.4 统计学分析

使用SPSS 26.0软件对血药浓度、基线数据、药代数据进行统计学分析处理;符合正态分布的资料以$\bar{x}\pm s$表示,并对数据资料进行独立样本t检验;非正态分布资料以$M(P_{25},P_{75})$表示,采用Mann-Whitney U检验;分类变量采用皮尔逊卡方检验。以$P<0.05$表示差异具有统计学意义。

2 结果

2.1 一般情况

在入组的90例患者中,8例因部分时间点血液样本污染(含1例麻醉时间不足2 h)不纳入药代分析,最终得到了82例患者的820份血浆药物浓度数据。其中,Ⅰ类患者中低体质量1例(BMI=18.3 kg/m^2)、正常体质量13例、超重13例;Ⅱ类患者中低体质量1例(BMI=18 kg/m^2)、正常体质量13例、超重12例、肥胖1例(BMI=28 kg/m^2);Ⅲ类患者中正常体质量15例、超重13例;纳入正常体质量组和超重组分析的患者共79例。患者术中麻醉满意手术顺利,无麻醉手术相关并发症发生。正常体质量人群与超重人群相比,BMI和体质量均有统计学差异($P<0.001$,表2)。

2.2 舒芬太尼在Ⅰ-Ⅲ类人群不同BMI患者的平均血浆药物浓度-时间曲线

舒芬太尼在体内的药代动力学行为符合二室模型。Ⅰ-Ⅲ类人群不同BMI患者的平均血浆药物浓度-时间曲线结果显示,Ⅰ类人群在舒芬太尼单次推注2 min时超重组血药浓度显著高于正常体质量组($P<0.000\ 1$)。Ⅱ类人群前5 min两组的平均血浆药物浓度各时间点差异无统计学意义。Ⅲ类人群在舒芬太尼单次推注2 min时超重组血药浓度显著高于正常体质量组($P<0.001$,图1)。

2.3 正常体质量组和超重组舒芬太尼药物代谢动力学参数差异

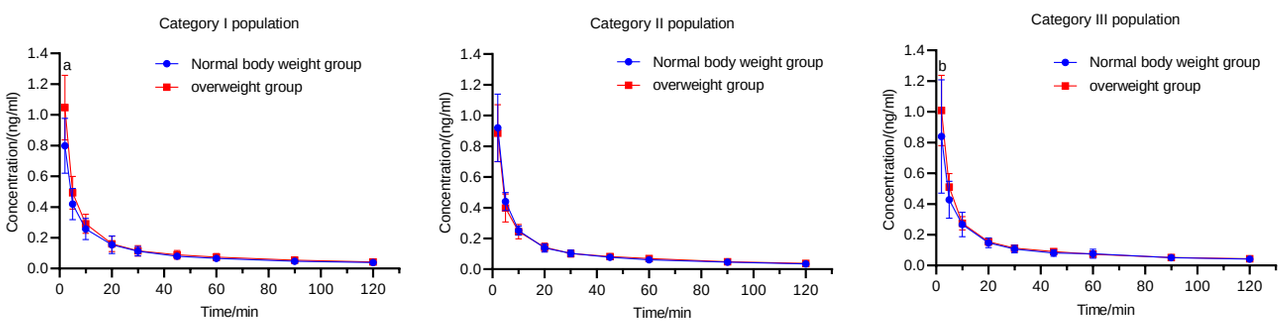
对正常体质量组和超重组患者的药代动力学参数进行比较,结果见表3。正常体质量组的V_1显著高于超重组($P=0.019$)。超重组的V_2、CL、CL_2、$t_{1/2\alpha}$、$t_{1/2\beta}$均小于正常体质量组,但差异未达到统计学意义;AUC_{0-t}、$AUC_{0-\infty}$均大于正常体质量组,但差异不具有统计学意义。

表2 正常体质量组和超重组一般情况比较[n=79,$\bar{x}\pm s$,$M(P_{25},P_{75})$]

Table 2 Comparison of general information between the normal body weight group and the overweight group [n=79,$\bar{x}\pm s$,$M(P_{25},P_{75})$]

Item	Normal body weight group(n=41)	Super recombination(n=38)	$Z/t/\chi^2$	P
Age/years	51.00(48.00,54.00)	52.50(46.00,55.25)	0.595	0.552
Gender(Male/Female)	21/20	19/19	0.012	0.914
Height/cm	160.40±6.83	159.78±7.21	0.393	0.695
Weight/kg	56.18±6.78	65.06±6.22	−6.074	<0.001
BMI/(kg/m^2)	21.70(20.40,22.95)	25.50(24.40,26.60)	−7.647	<0.001
Total intake/mL	1 250(1 000,1 700)	1 200(1 100,1 625)	−0.587	0.557
Net inflow/mL	280.0(160.0,420.0)	275.0(97.5,405.0)	−0.687	0.492
Urine volume/mL	200(120,300)	300(200,300)	−1.343	0.179
Blood loss volume/mL	120.00(50.00,152.50)	105.00(57.50,188.75)	−0.177	0.859
Serum creatinine/(μmol/L)	67.40(61.05,77.65)	67.15(61.97,78.90)	−0.402	0.687
Estimate glomerular filtration rate(mL/min·1.73m^2)	95.22±16.74	93.35±17.46	0.485	0.629
ASA classification(Ⅰ/Ⅱ)	1/40	0/38		

BMI: Body mass index; Total intake: Crystals+colloids+blood products; Net intake: Total intake-urine volume-blood loss-hidden water loss



a: P<0.0001, b: P<0.001

图1 I-III类人群不同BMI患者的平均血浆药物浓度-时间曲线

Figure 1 Average plasma drug concentration-time curves of patients with different BMI levels in groups I-III

表3 正常体质量组和超重组药代动力学参数比较[n=79,$\bar{x}\pm s$,$M(P_{25},P_{75})$]

Table 3 Comparison of pharmacokinetic parameters between normal phenotype group and hyper phenotype group [n=79,$\bar{x}\pm s$,$M(P_{25},P_{75})$]

Pharmacokinetic parameters	Normal body weight group(n=41)	Super recombination(n=38)	Z/t	P
V_1/(L/kg)	0.36(0.29,0.49)	0.31(0.23,0.41)	−2.345	0.019
V_2/(L/kg)	1.05(0.79,1.27)	0.91(0.71,1.01)	−1.491	0.136
CL/[L/(min·kg)]	0.034±0.008	0.031±0.007	1.638	0.105
CL_2/[L/(min·kg)]	0.06±0.02	0.05±0.01	1.913	0.060
$t_{1/2\alpha}$/min	2.28(1.90,2.66)	2.08(1.62,2.74)	−1.197	0.231
$t_{1/2\beta}$/min	38.22(31.67,48.57)	37.97(30.60,44.25)	−0.383	0.702
K10/(1/min)	0.09(0.06,0.12)	0.10(0.08,0.14)	−1.276	0.202
K12/(1/min)	0.17(0.14,0.20)	0.19(0.15,0.22)	−1.491	0.136
K21/(1/min)	0.06(0.05,0.07)	0.06(0.05,0.07)	−0.569	0.569
$AUC_{0\text{-}t}$/[(min·μg/L)]	14.95±3.17	16.22±3.41	−1.727	0.088
$AUC_{0\text{-}\infty}$/[(min·μg/L)]	18.28(15.87,21.03)	20.17(17.55,23.91)	−1.805	0.071

2.4 三类人群正常体质量组和超重组舒芬太尼药物代谢动力学参数差异

对Ⅰ、Ⅱ、Ⅲ类人群中不同BMI分组的患者接受舒芬太尼单剂量注射0.5 μg/kg后的药物代谢动力学参数进行统计学分析。结果表明,Ⅰ类人群中正常体质量组的V_1、V_2和CL_2均显著大于超重组(P<0.05),CL、$t_{1/2\alpha}$、$t_{1/2\beta}$、AUC_{0-t}、$AUC_{0-\infty}$的差异无统计学意义(表4)。Ⅱ、Ⅲ类人群药物代谢动力学参数比较差异无统计学意义(表5、6)。

3 讨论

3.1 超重人群与正常体质量人群药物代谢差异

舒芬太尼在超重人群中表现出与正常体质量人群一致的代谢能力。舒芬太尼作为高脂溶性、高血浆蛋白结合率(约90%)的阿片类药物,其药代特性为这一现象提供了潜在解释。既往研究指出体质量增加可能通过改变脂溶性药物的脂肪-血浆分配系数影响分布[16],然而舒芬太尼的高蛋白结合特性可能限制了其向组织的扩散,从而缓冲了脂肪蓄积对分布容积的显著影响[17]。此外,其主要通过肝脏CYP3A代谢清除,而超重相关的肝酶活性变化可能尚未达到显著改变其代谢速率的阈值[18]。值得注意的是,当BMI发生更显著的改变(如达到肥胖程度)时,伴随的肝脏血流动力学变化则可能产生具有临床意义的清除率差异[19]。因此,本研究基于BMI分层的数据支持将正常体质量与超重人群在舒芬太尼代谢层面归为一类,与肥胖人群区分,这为临床实践中舒芬太尼的用药人群划分提供了新视角。尤其值得关注的是,本研究观察

表4 Ⅰ类人群不同BMI患者药代动力学参数比较[$\bar{x}\pm s$,$M(P_{25},P_{75})$]

Table 4 Comparison of pharmacokinetic parameters in patients of different BMI level within the first category population [$\bar{x}\pm s$,$M(P_{25},P_{75})$]

Pharmacokinetic parameters	Normal body weight group(n=13)	Super recombination(n=13)	Z/t	P
V_1/(L/kg)	0.36(0.32,0.49)	0.27(0.23,0.36)	−2.487	0.013
V_2/(L/kg)	1.00±0.29	0.79±0.14	2.309	0.030
CL/[L/(min·kg)]	0.04±0.01	0.03±0.01	1.243	0.226
CL_2/[L/(min·kg)]	0.07±0.02	0.05±0.01	2.589	0.016
$t_{1/2\alpha}$/min	2.33±0.70	2.09±0.60	0.946	0.354
$t_{1/2\beta}$/min	36.98±10.02	34.33±6.85	0.787	0.439
K10/(1/min)	0.09±0.03	1.12±0.05	−1.599	0.123
K12/(1/min)	0.18±0.06	0.19±0.05	−0.596	0.557
K21/(1/min)	0.07(0.06,0.07)	0.06(0.05,0.07)	−0.385	0.701
AUC_{0-t}/[(min·μg/L)]	14.49±3.22	16.82±3.28	−1.835	0.079
$AUC_{0-\infty}$/[(min·μg/L)]	18.20±3.88	20.88±4.59	−1.608	0.121

表5 Ⅱ类人群不同BMI患者药代动力学参数比较[$\bar{x}\pm s$,$M(P_{25},P_{75})$]

Table 5 Comparison of pharmacokinetic parameters in patients of different BMI within the second category population [$\bar{x}\pm s$,$M(P_{25},P_{75})$]

Pharmacokinetic parameters	Normal body weight group(n=13)	Super recombination(n=13)	Z/t	P
V_1/(L/kg)	0.34±0.12	0.32±0.14	0.429	0.672
V_2/(L/kg)	0.86(0.63,1.08)	1.04(0.74,1.13)	−0.979	0.328
CL/[L/(min·kg)]	0.03±0.01	0.03±0.01	0.485	0.632
CL_2/[L/(min·kg)]	0.05(0.05,0.07)	0.06(0.05,0.08)	−0.761	0.446
$t_{1/2\alpha}$/min	2.12±0.39	2.04±0.92	0.286	0.778
$t_{1/2\beta}$/min	33.97±9.83	37.26±10.45	−0.809	0.427
K10/(1/min)	0.11(0.08,0.14)	0.11(0.06,0.16)	−0.054	0.957
K12/(1/min)	0.18±0.04	0.24±0.12	−1.623	0.118
K21/(1/min)	0.07±0.02	0.06±0.01	−0.754	0.459
AUC_{0-t}/[(min·μg/L)]	15.23±2.24	15.69±4.16	−0.344	0.734
$AUC_{0-\infty}$/[(min·μg/L)]	17.82(17.50,21.53)	18.65(16.04,23.42)	−0.016	0.870

表6 Ⅲ类人群不同BMI患者药代动力学参数比较[$\bar{x}\pm s$,$M(P_{25},P_{75})$]

Table 6 Comparison of pharmacokinetic parameters in patients of the third category with different BMI levels [$\bar{x}\pm s$,$M(P_{25},P_{75})$]

Pharmacokinetic parameters	Normal body weight group(n=13)	Super recombination(n=13)	Z/t	P
V_1/(L/kg)	0.44±0.22	0.32±0.09	1.858	0.075
V_2/(L/kg)	1.21±0.36	1.05±0.32	1.185	0.247
CL/[L/(min·kg)]	0.03±0.01	0.03±0.01	1.112	0.276
CL_2/[L/(min·kg)]	0.06±0.02	0.05±0.01	1.368	0.183
$t_{1/2\alpha}$/min	2.62(2.06,3.01)	2.26(2.00,2.85)	−0.898	0.369
$t_{1/2\beta}$/min	47.28(35.25,56.67)	47.18(31.84,52.82)	−0.668	0.504
K10/(1/min)	0.07(0.06,0.10)	0.09(0.08,0.11)	−1.359	0.174
K12/(1/min)	0.16±0.05	0.17±0.04	−0.590	0.561
K21/(1/min)	0.05±0.02	0.05±0.02	0.198	0.845
AUC_{0-t}/[(min·μg/L)]	15.10±3.91	16.12±2.93	−0.776	0.445
$AUC_{0-\infty}$/[(min·μg/L)]	18.81(15.82,20.56)	21.55(17.59,24.34)	−1.543	0.123

到在正常至超重的BMI范围内,随着BMI增加,舒芬太尼的代谢能力呈现降低趋势,主要表现为分布容积、清除率和半衰期的减小,这提示在目前的临床工作中根据患者的TBW计算舒芬太尼的诱导剂量会增加患者的不良反应,表现为超重人群的药物暴露量更大即AUC曲线下面积较正常体质量人群增大。在临床中使用舒芬太尼进行镇痛治疗时,建议可对超重人群也引入肥胖患者麻醉专家共识主张的按理想体质量(ideal body weight, IBW)或瘦体质量(lean body weight, LBW)来计算诱导剂量,以减少围术期患者阿片类药物的不良反应。

3.2 三类人群中超重人群与正常体质量人群药物代谢差异

深入分析不同基因型组合人群的药物代谢参数结果发现,CYP3A4纯合突变或CYP3A4杂合突变复合CYP3A5纯合突变人群中,超重比正常体质量组的V_1、V_2更小,CL_2更低(P<0.05),这可通过超重的生理改变解释:脂肪细胞增生形成低血流灌注的疏松脂肪组织,限制了药物向外周室的分布,导致V_2降低[20];同时超重引起的舒芬太尼蛋白结合率增高导致中央室游离药物减少,V_1缩小,肌肉组织低灌注进一步限制了药物分布即V_2下降及代谢清除即CL_2下降[21]。然而关键的药物代谢参数CL、$t_{1/2\alpha}$、$t_{1/2\beta}$、AUC_{0-t}、$AUC_{0-\infty}$在两组间无统计学差异,因此该基因型组合下超重与正常体质量患者的总体代谢能力无实质性差别;在3A4杂合突变复合3A5杂合突变、3A4野生型或3A4杂合突变复合3A5野生型人群中,超重和正常体质量人群的药物代谢能力同样未显示出差异。CYP3A4酶是定位于7q22.1染色体、含13个外显子的核心药物代谢酶,其负责了包括芬太尼类在内约50%临床药物的生物转化作用[22],其基因多态性如东亚人群高频功能突变位点CYP3A4*1G可显著影响酶活性[23,24],体外研究已证实*CYP3A4 *1G*等位基因与多种阿片类药物在肝微粒体中的代谢差异有关[25]。值得注意的是,虽然本研究在特定基因型组合中未发现超重对代谢能力的显著影响,但既往证据表明BMI增大可下调CYP3A4酶活性[26],特别是在CYP3A4*1G携带者中可能改变其药代特征(如延长$t_{1/2\beta}$、降低代谢速率、增加蓄积风险)。KROGSTAD等[27]的研究也提示体质量增加会降低CYP3A底物的清除率。在CYP3A4纯合突变或CYP3A4杂合突变复合CYP3A5纯合突变人群中,与超重状态可能通过减少分布容积(源于组织灌注改变及蛋白结合率升高)产生交互作用,潜在提高血药浓度,加剧代谢障碍风险(如呼吸抑制),尽管在本研究特定基因型组合和BMI分层下未观察到对最终清除率和暴露量的显著影响。

3.3 研究局限性及未来研究方向

本研究存在若干局限性:①采用外周静脉采血法可能低估动脉峰浓度,影响最大血浆药物浓度及AUC_{0-t}计算的准确性[28]。②作为一项二次分析研究,样本量相对有限(n=79)且受试者年龄范围(18~59岁)未能覆盖更广泛人群。③研究聚焦于CYP3A酶系,未系统考察肝脏中其他重要药物代谢酶(如CYP2D6)的活性变化[29],这些酶系的潜在改变也可能影响舒芬太尼的代谢途径。④采样时间方面在120 min停止采血,可能未充分捕捉消除相数据,导致估算的药代学数据出现偏差。未来研究应致力于扩大样本量,纳入不同年龄段(如老年、青少年)受试者,并综合评估多种药物代谢酶的活性,密集采血时间扩大采血时限以构建更精准的个体化用药模型。

综上所述,本研究创新性地采用口腔咽拭子无创快速基因检测技术对*CYP3A4*和*CYP3A5*基因多态性进行分析,并探讨不同基因型组合人群BMI分层对舒芬太尼药代动力学的影响,研究结果显示在携带特定CYP3A4/5突变程度基因型组合人群,超重和正常体质量患者舒芬太尼代谢能力无差异,另外与正常体质量个体相比,CYP3A4纯合突变或CYP3A4杂合突变复合CYP3A5纯合突变人群中超重患者舒芬太尼的外周室分布范围更小,且代谢过程显著减弱,为临床针对该类人群制定舒芬太尼个体化用药方案、保障用药安全提供了关键实践依据。基于此发现,在舒芬太尼单次静脉注射镇痛的临床实践中,针对此类特定基因型组合的非肥胖患者(包括正常体质量和超重人群),制定初始给药方案时可能无需特别考量超重因素对药物代谢清除过程本身的干扰。在临床用药中应重点监测镇痛效果,若超重出现镇痛不足需谨慎增量,而非盲目加量,同时密切关注呼吸抑制、嗜睡、恶心呕吐等不良反应,监测时长需较正常体质量人群延长。本研究结论严格基于单次给药下的二室模型药代动力学分析,其参数及推导结果不能直接外推用于指导持续输注状态下的剂量调整。持续输注涉及复杂的药物分布、潜在累积效应及代谢等问题,需进行专门研究。此外,临床实践中仍需警惕超重可能通过改变分布容积等途径影响药物初始效应,以及基因型与环境因素潜在的交互作用对个体安全性的影响。

利益冲突 本文所有作者声明不存在利益冲突

参考文献:

[1] GUAN Y C, WANG H C, CONG X J, *et al*. Effect of esketamine compared with sufentanil combined with propofol in patients undergoing first trimester surgical abortion: a randomized, double-blinded clinical trial[J]. Drug Des Devel Ther, 2025, 19: 2873-2883. DOI:10.2147/DDDT.S515006.

[2] GAO W, SHA B Y, ZHAO Y, *et al*. Comparison of simultaneous and sequential administration of fentanyl-propofol for surgical abortion: a randomized single-blinded controlled trial[J]. Artif Cells Nanomed Biotechnol, 2017, 45(5): 1045-1050. DOI:10.1080/21691401.2016.1239106.

[3] GOKHALE P, LAPPEN J R, WATERS J H, *et al*. Intravenous sedation without intubation and the risk of anesthesia complications for obese and non-obese women undergoing surgical abortion: a retrospective cohort study[J]. Anesth Analg, 2016, 122(6): 1957-1962. DOI: 10.1213/ANE.0000000000001335.

[4] 王天龙, 黄宇光. 推动麻醉学向围手术期医学转变:《加速康复外科中国专家共识及路径管理指南(2018版)》麻醉部分解读[J]. 协和医学杂志, 2018, 9(6): 481-484. DOI:10.3969/j.issn.1674-9081.2018.06.001.
WANG T L, HUANG Y G. Campaigning for the transformation from anesthesiology to perioperative medicine: interpretation on the anesthesia part of consensus on ERAS and guidelines for the pathway management in China (2018)[J]. Med J Peking Union Med Coll Hosp, 2018, 9(6): 481-484. DOI:10.3969/j.issn.1674-9081.2018.06.001.

[5] 何姗, 王永徽, 路志红. 右美托咪定用于梗阻性黄疸患者术后镇痛的有效性和安全性研究[J]. 空军军医大学学报, 2025, 16(2): 232-235. DOI: 10.13276/j.issn.2097-1656.2025.02.016.
HE S, WANG Y H, LU Z H. Efficacy and safety of dexmedetomidine for postoperative analgesia in patients with obstructive jaundice[J]. J Air Force Med Univ, 2025, 16(2): 232-235. DOI: 10.13276/j.issn.2097-1656.2025.02.016.

[6] RAHMIOGLU N, HEATON J, CLEMENT G, *et al*. Genetic epidemiology of induced CYP3A4 activity[J]. Pharmacogenet Genomics, 2011, 21(10): 642-651. DOI: 10.1097/FPC.0b013e3283498ecf.

[7] ZHANG T, CALVIER E A M, KREKELS E H J, *et al*. Impact of obesity on hepatic drug clearance: what are the influential variables?[J]. AAPS J, 2024, 26(3): 59. DOI: 10.1208/s12248-024-00929-3.

[8] 中华人民共和国国家卫生健康委员会医政司. 肥胖症诊疗指南(2024年版)[J]. 中华消化外科杂志, 2024, 23(10): 1237-1260. DOI: 10.3760/cma.j.cn115610-20241017-00455.
Department of Medical Administration, National Health Commission of the People's Republic of China. Guideline for diagnosis and treatment of obesity (2024 edition)[J]. Chin J Dig Surg, 2024, 23(10): 1237-1260. DOI: 10.3760/cma.j.cn115610-20241017-00455.

[9] NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults[J]. Lancet, 2024, 403(10431): 1027-1050. DOI: 10.1016/S0140-6736(23)02750-2.

[10] HURT R T, KULISEK C, BUCHANAN L A, *et al*. The obesity epidemic: challenges, health initiatives, and implications for gastroenterologists[J]. Gastroenterol Hepatol, 2010, 6(12): 780-792.

[11] GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019[J]. Lancet, 2020, 396(10258): 1223-1249. DOI:

10.1016/S0140-6736(20)30752-2.

[12] KAHAN S. Overweight and obesity management strategies [J]. Am J Manag Care, 2016, 22(7 Suppl): s186-s196.

[13] NOTHOFER S, HASELBECK-KOEBLER M, ZEITLINGER M, *et al*. Surgical antibiotic prophylaxis dosing in adult patients with obesity: a comprehensive review of pharmacokinetic and pharmacodynamic data [J]. Anesthesiology, 2025, 142(5): 929-948. DOI: 10.1097/aln.0000000000005410.

[14] BARRAS M, LEGG A. Drug dosing in obese adults [J]. Aust Prescr, 2017, 40(5): 189-193. DOI: 10.18773/austprescr.2017.053.

[15] 蒋颖, 秦志刚, 冯力元, 等. CYP3A酶突变类型与舒芬太尼代谢的性别差异研究[J]. 陆军军医大学学报, 2025, 47(6): 581-590. DOI:10.16016/j.2097-0927.202501002.
JIANG Y, QIN Z G, FENG L Y, *et al*. Mutation types of CYP3A enzymes and sex differences in sufentanil metabolism[J]. J Army Med Univ, 2025, 47(6): 581-590. DOI:10.16016/j.2097-0927.202501002.

[16] BRUNO C D, HARMATZ J S, DUAN S X, *et al*. Effect of lipophilicity on drug distribution and elimination: Influence of obesity[J]. Br J Clin Pharmacol, 2021, 87(8): 3197-3205. DOI:10.1111/bcp.14735.

[17] SCHOLZ J, STEINFATH M, SCHULZ M. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil[J]. Clin Pharmacokinet, 1996, 31(4): 275-292. DOI:10.2165/00003088-199631040-00004.

[18] GHOBADI C, JOHNSON T N, AARABI M, *et al*. Application of a systems approach to the bottom-up assessment of pharmacokinetics in obese patients[J]. Clin Pharmacokinet, 2011, 50(12): 809-822. DOI: 10.2165/11594420-000000000-00000.

[19] ZHANG T, KREKELS E H J, SMIT C, *et al*. Drug pharmacokinetics in the obese population: challenging common assumptions on predictors of obesity-related parameter changes[J]. Expert Opin Drug Metab Toxicol, 2022, 18(10): 657-674. DOI: 10.1080/17425255.2022.2132931.

[20] BIENERT A, MOOR A B, OKUŃSKA P, *et al*. Pharmacokinetics of sufentanil after epidural administration during the course of extensive abdominal surgery[J]. Clin Pharmacokinet, 2025, 64(9): 1331-1340. DOI: 10.1007/s40262-025-01543-y.

[21] 黄泽汉. 舒芬太尼的药理学和临床应用进展[J]. 右江民族医学院学报, 2009, 31(6): 1057-1058. DOI:10.3969/j.issn.1001-5817.2009.06.085.
HUANG Z H. Progress in pharmacology and clinical application of sufentanil[J]. J Youjiang Med Coll Natl, 2009, 31(6): 1057-1058. DOI:10.3969/j.issn.1001-5817.2009.06.085.

[22] 刘璐萍, 黄剑, 方芳, 等. CYP3A4、CYP3A5、COMT及OPRM1基因多态性对术后芬太尼镇痛剂量的影响[J]. 中国临床医学, 2023, 30(5): 785-791. DOI:10.12025/j.issn.1008-6358.2023.20230922.
LIU L P, HUANG J, FANG F, *et al*. Correlation between *CYP3A4*/*CYP3A5*/*COMT*/OPRM1 gene polymorphisms and postoperative fentanyl requirements[J]. Chin J Clin Med, 2023, 30(5): 785-791. DOI: 10.12025/j.issn.1008-6358.2023.20230922.

[23] MCMILLAN D M, EL-SHERBENI A A, RICHARDS J, *et al*. Centrally administered CYP2D inhibitors increase oral tramadol analgesia in rats[J]. Brain Res Bull, 2020, 164: 400-406. DOI:10.1016/j.brainresbull.2020.09.001.

[24] ZHANG W, YUAN J J, KAN Q C, *et al*. Influence of CYP3A5*3 polymorphism and interaction between CYP3A5*3 and CYP3A4*1G polymorphisms on post-operative fentanyl analgesia in Chinese patients undergoing gynaecological surgery[J]. Eur J Anaesthesiol, 2011, 28(4): 245-250.

[25] TUET W Y, PIERCE S A, CONROY M, *et al*. Metabolic clearance of select opioids and opioid antagonists using hepatic spheroids and recombinant cytochrome P450 enzymes [J]. Pharmacol Res Perspect, 2022, 10(5): e01000. DOI:10.1002/prp2.1000.

[26] KVITNE K E, ROBERTSEN I, SKOVLUND E, *et al*. Short- and long-term effects of body weight loss following calorie restriction and gastric bypass on CYP3A-activity - a non-randomized three-armed controlled trial[J]. Clin Transl Sci, 2022, 15(1): 221-233. DOI:10.1111/cts.13142.

[27] KROGSTAD V, PERIC A, ROBERTSEN I, *et al*. Correlation of body weight and composition with hepatic activities of cytochrome P450 enzymes[J]. J Pharm Sci, 2021, 110(1): 432-437. DOI:10.1016/j.xphs.2020.10.027.

[28] FISHER D M, CHANG P, WADA D R, *et al*. Pharmacokinetic properties of a sufentanil sublingual tablet intended to treat acute pain[J]. Anesthesiology, 2018, 128(5): 943-952. DOI:10.1097/aln.0000000000002145.

[29] STAVROPOULOU E, PIRCALABIORU G G, BEZIRTZOGLOU E. The role of cytochromes P450 in infection[J]. Front Immunol, 2018, 9: 89. DOI: 10.3389/fimmu.2018.00089.

(**收稿**:2025-09-01;**修回**:2025-11-14)

(编辑 刘秋池)