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瑞马唑仑在无痛气管镜中的GABAA受体作用机制及其临床优势

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摘　要

由于社会发展以及医疗舒适化，无痛气管镜检查已成为呼吸系统疾病诊断和治疗的常用方法。瑞马唑仑作为一种新型超短效镇静药物，凭借其快速起效、迅速恢复、不良反应少等药理学特性，展现出其在无痛气管镜中较高的成功率、呼吸循环的稳定性、苏醒质量以及术后认知功能恢复等方面的优势。本文综述了瑞马唑仑在无痛气管镜中的GABAA受体作用机制及其临床应用优势，未来随着联合用药方案的优化，瑞马唑仑有望进一步推动气管镜镇静进入智能化、个体化时代。

关键词

瑞马唑仑，无痛气管镜，GABAA受体

The Mechanism of Action of Remimazolam on GABAA Receptors in Painless Bronchoscopy and Its Clinical Advantages

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Abstract

Due to societal development and the trend toward patient comfort in medical care, pain-free bronchoscopy has become a commonly used method for the diagnosis and treatment of respiratory

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system diseases. Remimazolam, as a novel ultra-short-acting sedative drug, demonstrates its advantages in pain-free bronchoscopy due to its pharmacological characteristics, including rapid onset of action, swift recovery, and minimal adverse effects. These characteristics contribute to its high success rate, stability of respiratory and circulatory functions, quality of awakening, and improved post-operative cognitive function recovery. This article reviews the GABAA receptor mechanism of action of remimazolam in pain-free bronchoscopy and its clinical application advantages. In the future, with the optimization of combination therapy regimens, remimazolam is expected to further drive the advancement of bronchoscopy sedation into an era of intelligence and individualization.

Keywords

Remimazolam, Painless Bronchoscopy, GABAA Receptor

1. 引言

气管镜检查作为呼吸系统疾病诊疗的重要手段，其操作过程中患者的安全与舒适始终是临床关注的焦点。传统的气管镜镇静面临诸多挑战，包括呼吸抑制、血流动力学波动以及苏醒延迟等问题[1]。特别是在手术室外进行的操作，镇静药物常常需要满足快速起效、精确可控和迅速恢复等要求[2]。已有研究表明使用传统镇静药物的患者中，约 30%在气管镜检查期间会出现氧饱和度下降等呼吸相关不良事件[3] [4]，这也说明临床上对更安全的镇静方案有着迫切需求。

从长效药物地西泮到中效的咪达唑仑，在镇静药物的发展历程中研究者们始终努力优化药代动力学特性[5]。虽然较以往药物有了一定改进，但咪达唑仑仍存在作用时间较长、个体差异大等不足[1] [6]。而新型苯二氮卓类药物瑞马唑仑的出现，凭借其经组织酯酶代谢的特点，实现了超短效的效果[7] [8]，同时保留了苯二氮卓类药物本身具有的抗焦虑和顺行性遗忘优点[9]。这一发展体现了镇静药物从长效不可控向短效精确调控的转变趋势[10]。

瑞马唑仑作为新型苯二氮卓类药物，通过特异性作用于 GABAA 受体产生镇静效果[11]，与其他麻醉药物相比，它展现出三大优势：一是通过组织酯酶代谢，这种代谢途径不依赖特定器官[12]，即便肝功能受损患者也能安全使用；二是独特的水溶性，使其注射时不会产生疼痛[12]，患者的用药体验得到了改善；三是临床数据显示其呼吸循环抑制的概率明显低于丙泊酚和咪达唑仑[9] [13]。在气管镜检查中，使用瑞马唑仑能明显缩短气管镜操作开始时间(平均缩短 5.2 分钟)，且操作成功率高达 80.6%，远高于传统药物[4]。氟马西尼可快速逆转其作用的特点[14]，为临床提供了额外的安全保障。

2. GABAA 受体作用机制

2.1. 受体亚基选择性结合特征

新型苯二氮卓类药物瑞马唑仑对 GABAA 受体表现出高度选择性，它作用于该受体而不影响其他神经递质系统[4]。研究表明其具有显著的亚基结合偏好性，主要通过与 $\alpha 1$ 和 $\alpha 5$ 亚型结合发挥镇静作用[15]。这种选择性结合模式较第一代苯二氮卓类药物能产生更精准的镇静效果，不会引起过度肌松或认知功能障碍[16]。在受体亚基表达谱分析中发现，瑞马唑仑对 $\alpha 3$ 亚基的表达影响较小，这可能与其在脊髓

背角镇痛作用中的独特表现相关[10]。临床前研究证实 $\alpha 1$ 亚型的选择性激活与其快速起效特性密切相关[5]。

2.2. 变构调节与氯离子通道开放动力学

瑞马唑仑通过变构调节机制增强 GABAA 受体功能，作为正性变构调节剂促进 γ-氨基丁酸与受体的结合[17]。这种调节方式使氯离子通道开放动力学发生变化，表现为通道开放频率增加而单次开放持续时间不变[18]。与传统的苯二氮卓类药物相比，瑞马唑仑引起的通道变构调节具有更快的结合–解离速率，这与其超短效的药理学特性直接相关[19]。电生理研究显示，该药物对突触外 GABAA 受体(含 δ 亚基)的调节作用较弱，这可能与其呼吸抑制轻微相关[20]。上述研究主要基于动物模型或离体实验，虽揭示了瑞马唑仑对 GABAA 受体氯离子通道的调控机制，但其结论应用到气管镜仍需进一步验证，气管镜检查中患者呼吸抑制风险受到多种因素影响，包括体位、操作刺激、联合用药等，因此瑞马唑仑在临床实践中展现出的呼吸稳定性可能来源于多项因素共同结果。通过这种独特的变构调节方式，瑞马唑仑能够在维持足够镇静深度的同时保持较好的血流动力学稳定[21]。

2.3. 与丙泊酚/右美托咪定的作用位点差异

与丙泊酚直接激活 GABAA 受体的作用机制不同，瑞马唑仑通过经典的苯二氮卓结合位点发挥作用[15]。这种位点差异导致二者在受体激活模式上存在显著区别：丙泊酚主要增强强直性抑制，而瑞马唑仑更倾向于调节相位性抑制[18]。与右美托咪定相比，瑞马唑仑不作用于 $\alpha 2$ 肾上腺素能受体，因此不会产生中枢性抗交感效应[17]。分子对接研究表明，瑞马唑仑的结合口袋较传统苯二氮卓类药物更浅，这可能是其能够被氟马西尼快速逆转的结构基础[17]。这种作用位点的特异性也使得瑞马唑仑在维持足够镇静状态的同时又较少引起血流动力学波动[22]。

3. 药代动力学特性与临床应用

3.1. 酯酶代谢途径的短效性基础

瑞马唑仑作为一种新型超短效苯二氮卓类药物，其独特的代谢特性源于组织酯酶介导的水解途径。和传统依赖肝脏代谢的药物不同，瑞马唑仑能通过血浆和组织中的非特异性酯酶，快速代谢为无活性的羧酸代谢物 CNS7054 [21] [23]。这种酯酶代谢方式，让它具备了不依赖特定器官的特性，即使在肝肾功能受损患者中，代谢速率也能保持稳定[24]。临床研究表明，这种代谢机制使得瑞马唑仑的平均消除半衰期明显短于咪达唑仑(37~53 分钟 vs 2~5 小时)，为气管镜等短时操作提供了理想的药代动力学基础[5] [8]。

3.2. 血脑屏障穿透速率与起效时间

瑞马唑仑由于其高水溶性能够快速通过血脑屏障，静脉给药后平均 1~2 分钟就可起效[2] [21]。这种快速穿透中枢神经系统的特性和它分子结构中的亲水基团有关，既保持了对 GABAA 受体的高选择性又优化了体内的分布动力学[19] [21]。药效学研究显示，瑞马唑仑的血浆–效应室平衡半衰期约为 1.4 分钟，这种快速的生物相平衡使其能够实现精准的滴定给药，特别适合气管镜等需要快速调节镇静深度的操作[13] [25]。与丙泊酚相比，瑞马唑仑的血脑屏障穿透动力学更稳定，减少了因个体差异造成的起效时间不同[26] [27]。

3.3. 持续输注时的蓄积反应

de Jong 等人开展的临床药理学研究发现，瑞马唑仑的清除率(70~80 L/h)显著高于传统苯二氮卓类药物，且稳态分布容积较小(30~40 L)，这种特性使其即便长时间输注，恢复时间也能保持稳定[28]。其代谢

产物 CNS7054 的活性仅为原型药物的 1/400，这进一步降低了体内蓄积的风险[23] [29]。有研究针对持续 4 小时以上的输注情况进行观察，结果显示瑞马唑仑的恢复时间相比单次给药仅延长 20%~30%，远优于咪达唑仑的 3~5 倍延长[8] [21]。这种特性使其在需要延长镇静时间的气管镜治疗中具有特殊优势[30]。

4. 瑞马唑仑在无痛气管镜中的临床优势

4.1. 成功率与中断率

多项随机对照试验证实瑞马唑仑在无痛气管镜中优势显著。一项纳入 630 例患者的 Meta 分析显示，瑞马唑仑组镇静成功率(80.6%)明显高于安慰剂组(4.8%)和咪达唑仑组(32.9%) [31]。与丙泊酚相比，瑞马唑仑组的手术中断率更低(15.7% vs 4.1%) [32]，且气管镜操作开始时间更短[31]。在老年患者中，瑞马唑仑的镇静成功率与丙泊酚相近，但中断率明显更低[22] [27]。

4.2. 呼吸参数稳定性

瑞马唑仑在维持呼吸稳定性方面表现突出。Li 等人 Meta 分析显示，与丙泊酚相比，瑞马唑仑低氧血症发生率(RR: 0.36)和呼吸抑制风险(RR: 0.48)显著降低[33]。与右美托咪定相比，瑞马唑仑组的氧饱和度下降事件更少($P < 0.05$) [34]。AbuJwaid 等人进行了数据汇总，证明瑞马唑仑对呼吸的抑制作用明显小于咪达唑仑[35]，这与其独特的 GABAA 受体亚型选择性有关[16]。

4.3. 血流动力学稳定性

在血流动力学稳定性方面，瑞马唑仑展现出显著优势。与丙泊酚相比，瑞马唑仑组低血压发生率降低 55% (RR: 0.45) [33]。Zhang 等人发现，瑞马唑仑联合阿芬太尼使用时血流动力学参数波动幅度显著小于对照组[36]。多中心试验数据证实，瑞马唑仑在维持平均动脉压稳定性方面优于咪达唑仑($P < 0.001$) [31]，且心律失常发生率低于右美托咪定[37]。

4.4. 苏醒质量与术后认知保护

瑞马唑仑在苏醒质量和认知保护方面具有独特优势。Pastis 等人的研究显示其神经精神恢复时间较咪达唑仑缩短 30% [4]，且术后认知功能障碍发生率更低[38]。在老年患者中，瑞马唑仑组的苏醒质量评分显著优于丙泊酚组($P = 0.023$) [27]，这可能与其对 α5-GABAA 受体的选择性作用有关[39]。一项随机对照试验证实，瑞马唑仑不影响气管镜检查持续时间，但显著缩短诱导和恢复时间[35]，为手术室外麻醉提供了便利[16]。

5. 瑞马唑仑在无痛气管镜挑战中的精准应对

5.1. 咳嗽反射的抑制

气管镜操作直接刺激气道，常常引发咳嗽反射，影响操作顺利进行[40]。作为 GABAA 受体激动剂，瑞马唑仑通过中枢抑制作用降低气道敏感性[2]。与阿片类药物合用时可产生协同效应，显著增加咳嗽抑制效果[25]。研究显示，瑞马唑仑联合瑞芬太尼靶控输注可提高患者耐受性，减少术中咳嗽和体动[41]。

5.2. 维持自主呼吸

气管镜操作常需平衡镇静深度与呼吸抑制风险，避免低氧血症[42] [43]。与丙泊酚相比，瑞马唑仑显著降低低氧血症风险，尤其适用于保留自主呼吸的气管镜操作[42] [44]。其器官非依赖性代谢和短半衰期允许快速调整镇静深度，减少呼吸抑制累积效应[45]。

5.3. 操作刺激强度变化

气管镜操作中，在通过声门、隆突等敏感区时刺激增强，常需动态调整镇静深度[44]。瑞马唑仑的快速起效和恢复特性便于术中按需追加剂量以便应对刺激变化[46] [47]。相较于丙泊酚，瑞马唑仑显著减少低血压和心动过缓[44] [46]，更适合心血管高风险患者。

6. 特殊人群应用

6.1. 老年患者

瑞马唑仑在老年患者身上表现出独特的药效学特性。多项研究发现，其在老年心血管手术患者中并没有增加术后谵妄发生率，与丙泊酚对比展现出相当的认知安全性[48]。它在药效学上的敏感性可能与GABAA 受体α5 亚型的特殊调节作用有关，这种亚型在老年人大脑中的表达模式与年轻人存在差异[49]。老年患者使用瑞马唑仑后拔管时间和麻醉复苏室停留时间更长，在临床使用时可能需要适当调整给药方案[50]。在接受结肠癌根治术的老年患者中，使用瑞马唑仑的组别术后认知功能评估(MMSE 评分)高于丙泊酚组，其可能存在神经保护优势[51] [52]。气管镜操作本身可能影响通气功能，而瑞马唑仑的呼吸抑制较轻，更适合老年患者[44] [53]。

6.2. 呼吸功能受限患者

作为超短效苯二氮卓类药物，瑞马唑仑在呼吸功能受损患者中展现出一定的安全性。它通过组织酯酶代谢，不依赖肝肾功能，大大降低了呼吸抑制的风险[11]。在经导管主动脉瓣置换术(TAVI)等高风险手术中，瑞马唑仑能维持稳定的血流动力学，且未增加术后谵妄发生率[54]。但 TAVI 患者多为高龄、合并心血管疾病，其血流动力学机制可能和接受气管镜治疗患者不同，因此虽可借鉴其安全性数据，但在气管镜应用中仍需结合具体操作进行个体化评估。临床数据显示在接受下肢骨科手术的老年患者中，瑞马唑仑和右美托咪定相比，术后谵妄风险并没有显著升高，其在呼吸功能受限患者中可能存在潜在优势[55]。

6.3. 易发生术后谵妄患者

Park 等人通过 Meta 分析显示瑞马唑仑组术后谵妄发生率为 8.0%，与丙泊酚组的 10.4%没有统计学差异(OR: 0.74, 95% CI [0.39~1.42]) [51]。在心脏手术患者中，瑞马唑仑能维持合适的麻醉深度，减少脑电图爆发抑制现象，这可能有利于降低谵妄风险[56]。Kao 等人的系统评价证实，瑞马唑仑与术后短期认知功能改善有关，且手术类型对谵妄的发生影响很大[57]。ASA 分级、年龄和药物剂量是影响谵妄发生的关键因素，高风险人群使用时需谨慎[33]。改良电休克治疗(mECT)的案例报告提到，瑞马唑仑能有效控制术后兴奋状态，减少谵妄发生[58]，mECT 中的电刺激可能导致神经递质释放模式的改变进而影响瑞马唑仑的镇静–觉醒平衡，这与气管镜操作上存在本质区别，该结果在气管镜场景中的适用性仍需更多针对性研究支持。

7. 现存争议与局限性

目前在无痛气管镜操作中，瑞马唑仑的最佳联合用药方案仍存在临床争议。虽然已有研究证实其与阿芬太尼联用能维持患者自主呼吸下完成气管镜检查[36]，但与其他药物的协同效应还需要更多循证医学依据来支持。Zhou 等人在一项随机对照试验中得出结论，与丙泊酚相比，瑞马唑仑在呼吸循环抑制方面更具优势[30]，但联合用药时可能会改变它的药代动力学特性。不同研究中心采用的联合用药剂量差异明显，从 0.2 mg/kg 到诱导剂量不等[59]，这种剂量上的差异可能会导致对临床效果的评价不一致。老年患者对药物的敏感性会增强[60]，这类特殊人群需要进行个体化剂量调整。

作为 GABAA 受体的变构调节剂[61]，瑞马唑仑长期使用是否会引起受体减敏尚缺乏充分研究。虽然其代谢产物被认为无活性[12]，但类似结构的丙泊酚类似物代谢物可能产生神经生理学影响[62]。现有文献主要关注单次给药效果[12]，对于重复使用或持续输注情况下受体敏感性的变化尚未阐明。

瑞马唑仑通过 GABAA 受体激动发挥作用，具有器官非依赖性代谢和快速起效/恢复特点[2]。然而，其代谢产物的活性仍需进一步研究，可能与再镇静相关。在 6740 例接受瑞马唑仑的患者中，再镇静的发生率为 8 例，虽然发生率远低于低血压(911 例)或苏醒延迟(68 例)等不良事件[63]，但仍需关注其潜在风险，尤其是与其他药物联用。

8. 未来研究方向

瑞马唑仑独特的酯酶代谢特性以及对 GABAA 受体亚型的选择性，为它实现精准给药提供了理论支撑[5]。Shen 等人的研究发现，其血药浓度与镇静深度之间呈非线性关系，这为人工智能算法建模创造了条件[19]。未来研究可着眼于开发基于深度学习的闭环给药系统，通过实时整合脑电双频指数(BIS)、患者生理参数和药物代谢动力学数据，动态调整输注速率。现有证据显示氟马西尼对瑞马唑仑的拮抗存在作用时间不匹配情况，其半衰期明显短于瑞马唑仑活性代谢物[31]。这促使研究者探索开发缓释型氟马西尼制剂，比如纳米载体包裹技术和前药转化系统[64]。未来研究需重点解决两个关键问题：一是延长拮抗剂作用持续时间以预防“再镇静”现象[60]；二是优化分子结构以消除潜在的受体激动效应[65]。氟马西尼对 α5 亚型 GABAA 受体的特异性拮抗或许能成为改善术后认知功能的新靶点[66]。

9. 结论

瑞马唑仑作为新型超短效苯二氮卓类药物，通过选择性作用于 GABAA 受体(特别是 α1/α5 亚型)产生快速镇静效果，其独特的酯酶代谢方式，让它具备了起效迅速(约 1~2 分钟)、作用时间短(8~10 分钟)的药代动力学特性[66] [67]。在无痛气管镜中，多项随机对照试验证实其操作成功率明显高于传统药物如咪达唑仑(80.6% vs 32.9%)，且血氧饱和度下降事件的发生率降低了 40%以上[4] [35]。在血流动力学稳定性方面，和丙泊酚相比，使用瑞马唑仑时收缩压波动幅度减少 35%，尤其适用于老年及心血管高风险患者[5] [9]。未来研究应聚焦于人工智能给药系统开发等，进一步优化个体化用药方案[68]。现有证据支持瑞马唑仑可作为无痛气管镜的一线选择，但其在儿童群体中的应用还需更多安全性数据[69]。综上所述，瑞马唑仑在无痛气管镜中是一种安全、有效的镇静选择，尤其适用于老年、呼吸功能受限以及易发生术后谵妄患者。其快速起效、恢复快、不良反应少的特点使其优于传统镇静药物(如丙泊酚、咪达唑仑)。未来，随着联合用药方案的优化，瑞马唑仑有望进一步推动气管镜镇静进入智能化、个体化时代。

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