Discussion on the use of dizocine in the perioperative setting

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【**Abstract**】Summary to explore the use of dezocine in the perioperative period.

【**Key words**】Dizocine;Perioperative;Application

Dizocine as a novel opioid receptor agonist antagonist, fully agonistic κ Receptor, partial agonism μ Receptors, does not produce typical μ Receptor dependence, on δ Receptors also have some agonism. Because of its strong analgesic effect, poor dependence, and little side reactions, its application in the perioperative period has been paid more and more attention, and is now reviewed below.

1 Mechanism of action and pharmacokinetics of dezocine

Dizocine is a potent opioid with analgesic strength, onset, and duration of action comparable to morphine. Postoperative pain is relieved when the steady-state blood concentration exceeds 5-9 ng / ml, but adverse effects occur when the average peak concentration reaches 45 ng / ml; It can be absorbed quickly and completely after the injection, with a peak time of 10-90 min at 10 mg intramuscularly and a mean plasma concentration of 19 ng / ml (range 10-38 ng / ml). 10mg intravenously over 5min resulted in a mean terminal half-life of 2.4h (1.2-7. 4h), a mean volume of distribution of 10. 1l/kg (4. 7-20. 1l / kg) and a mean systemic clearance of 3. 3l/hr/kg (1.7-7. 2l / HR / kg).

2 Dizocine in general anesthesia

2.1 induction period

The use of dizocine in the induction phase of general anesthesia can inhibit the pharyngeal and cardiovascular reflexes caused by tracheal intubation and other adverse stress reactions [1], maintain circulatory stability and prevent fentanyl and sufentanil induced choking reactions [2-3], and the specific mechanism may be associated with the following factors [4-6]. ① dizocine acts on the C receptor of the bronchi to exert a constrictive effect on tracheal smooth muscle against sunitinib and ② Reduce the release of histamine to suppress choking reactions; ③ Competitively prevents sufentanil binding to opioid receptors; ④ Effects produced by agonistic K receptors that inhibit fentanyl action on μ Agonistic effect of receptor, suppress choking reaction. Chiang guijoan et al [7] showed that while intubated in general anesthesia, intravenous dizocine (0. 2 mg / kg) was more effective than intravenous fentanyl (3 μ G / kg), which is more effective in suppressing the stress response to tracheal intubation under general anesthesia and maintaining a stable circulatory condition, which may be associated with dezocine agitation μ Receptors, antagonism κ Receptors, and inhibits PNE and serotonin reabsorption, reducing sympathetic adrenergic system reflexes are involved [8]. Studies by Li Guoli

[9] showed that 0. 2 mg / kg dizocine for amnesic analgesia slowly induced anaesthesia inhibited the stress response of tracheal intubation better than 2 μ G / kg fentanyl) with appropriate sedation scores and a low incidence of adverse effects.

2.2 Extubation period

Dizocine can obviously reduce the cardiovascular malignant reaction and agitation in the awakening period during extubation from general anesthesia. Yu Hong [10] and others intravenously injected different doses of dizocine 30 minutes before the end of laparoscopic gallbladder surgery, the results suggested that intravenous 0. 1 mg / kg dizocine could exert maximum analgesic effect before the disappearance of remifentanil's analgesic effect after discontinuation of general anesthetics, while avoiding stress reaction produced by painful stimulus after the end of surgery and reducing the incidence of adverse reactions during the awakening period of general anesthesia without affecting respiratory and circulatory indexes. Ametrine butan [11] and other studies confirmed that the use of 0. 07 mg / kg dizocine preemptively before induction of general anesthesia can significantly reduce the occurrence of postoperative agitation, and can reduce postoperative BP and HR and other cardiovascular effects, while it can significantly relieve postoperative pain and obviously reduce postoperative adverse effects in patients. In addition, different modes of administration also affect the role of dezocine on postoperative adverse effects of general anesthesia. Shao Tao [12] used patients undergoing laparoscopic gallbladder surgery under remifentanil compound anesthesia to administer dezocine 0. 2 mg / kg intramuscularly or intravenously 30 min before the end of the surgery, and found that dizocine intramuscularly 30 min before the end of the surgery, effectively attenuated hyperalgesia, shortened the time to awakening and extubation, improved postoperative analgesia and sedation, and had a good safety profile. In pediatrics, Yanjun Zhang [13] and others observed that preoperative intravenous bolus of 0. 05mg/kg and 0. 1mg/kg dizocine groups were both effective in reducing pediatric sevoflurane compound anesthesia awakening agitation, but intravenous bolus of 0. 05mg/kg dizocine was effective in reducing pediatric sevoflurane compound anesthesia awakening agitation with appropriate sedation intensity and did not prolong postoperative stay.

3 Use of neuraxial anesthesia

Neuraxial anesthesia patients in a state of wakefulness, the discomfort of anesthesia itself, the intraoperative traction reaction and the patient's fear of surgery, etc. , lead to patient tension anxiety, even a sensation of frequent death, very unfavorable to the smooth progress of surgery, therefore adjuvant medication is essential, dizocine as a new type of opioid receptor agonist antagonist has also been continuously tried in the clinic, studies have shown [14] intravenous dizocine 5 mg, It could decrease the BIS value after 10 min (BIS 90. 2 ± 3. 1, $P < 0. 05$) and had a sedative effect, which might follow the excitation of the central κ Receptors involved. Dizocine 5 mg compounded with midazolam 2 mg, resulted in decreased BIS values after 10 min (BIS 73. 1 ± 2. 9, $P < 0. 05$), 100% anterograde amnesia without significant respiratory depression, was safe and comfortable, and was suitable for sedation and analgesia in perioperative patients. However, because midazolam has a short half-life and a short duration of action, we found in this study that patients wake up about 30 min after a single injection with BIS > 90 and that intermittent administration can make the patients

sleep back, but the blood concentration fluctuates greatly, the hemodynamic effects are large, and it cannot completely ensure the elimination of the patients' adverse intraoperative memory, therefore, a single injection of dizocine combined with midazolam might be a more ideal method. Jing Hui Chen [15] and other studies found that: the single drug use dose of dizocine should be as less than 0. 2 mg / kg as possible, and the inhibitory effect of this dose on the respiratory function of the patient is relatively weak, and does not affect the plane of anaesthesia, thereby enabling the expected effects of anaesthesia to be achieved.

4 Use in nerve blocks

Nerve block has been widely used in surgeries where the lesions on the extremities or body surface are limited because of its unique features, such as small block size, minimal interference with the organism, and convenience in perioperative management, but it is also because of this characteristic that incomplete block often occurs intraoperatively and that dizocine can strengthen its anesthetic effect. 16 Shen Bao Qu é [16] found that brachial plexus block with the addition of a small amount of dizocine to a local anesthetic markedly accelerated the onset of anesthesia, Prolonging the block time and improving the success rate of anaesthesia. 5, 6 in addition, Wang Fu Xiang [17] and others made a clinical observation on the different modes of administration of dizocine found that the administration mode of dizocine regional adjuvant anaesthesia was better than that of intravenous adjuvant applied to nerve block anaesthesia, which may be related to its opioid receptors acting on the peripheral system

5 Use in day surgery

In recent years, daytime surgical anaesthesia has mostly been accomplished with CO administered opioids (fentanyl or sufentanil, etc.) such as propofol or sevoflurane, but intraoperative side effects such as respiratory depression, nausea and vomiting are easily observed. Currently, it is considered that low-dose intravenous dezocine 0. 1-0. 15mg/kg combined with propofol or sevoflurane can be safely and effectively applied in day surgery such as painless enteroscopy, ureteroscopy, hysteroscopy, electronic fiber bronchoscope and human flow surgery, which significantly reduces the cardiovascular reaction caused by operation, analgesia and sedation is complete and awakening is rapid.

6 Postoperative analgesia

Dizocine can be used alone for postoperative analgesia. 18 Gao Guang Wu et Al18 administered dizocine 0. 1 mg / kg or sufentanil 1 intravenously to patients after surgery for thyroid cancer, respectively μ G / kg) was administered for analgesia the results suggested that there was no significant difference in VAS scores at each time point within 12 hours after surgery between the two groups. However, the incidence of adverse effects in the dezocine group was 26. 67% ($P > 0. 05$), The difference was 91.11% in sufentanil group ($P < 0. 05$). This is consistent with the findings of Xiaozhen Zheng et al. 19 in their study on postoperative analgesia with dizocine in elderly orthopedic surgery patients and Yin Liu et al. 20 in their study on postoperative intravenous analgesia with dizocine in pediatric otorhinolaryngology patients. 21, 22 the same Study21 separately compared 0. 80 mg / kg dizocine with 0. 01 mg / kg fentanyl in patients with gynecological malignancies and found that the, Its analgesic effect and suppression of postoperative stress response were superior to those of the

fentanyl group; And to some extent, they protect the organism's survival function, suggesting that compared with fentanyl, dizocine is more suitable for postoperative analgesia in patients with gynecologic malignancies. 22 in addition, Li Sheng liu22 showed that compared with fentanyl, dizocine analgesia has little effect on cognitive function and rapid postoperative recovery in elderly patients, which may be due to the fact that dizocine has no secondary distribution effect of fentanyl, and its drug elimination half-life is shorter than that of fentanyl, Accelerated the metabolism of drugs in the body, resulting in improved postoperative cognitive function.

Dizocine can be combined with opioids, NSAIDs, intravenous injections such as dexmedetomidine or postoperative intravenous controlled analgesia can reduce pure μ The dose of receptor opioid agonists, which reduce the occurrence of side reactions such as dizziness, somnolence, nausea, and vomiting, strengthen the sedative effect, strengthen the analgesic effect of NSAIDs, and effectively inhibit postoperative chills. 23-25 they can also be used in combination with dexamethasone and ropivacaine for postoperative self-controlled analgesia with local infiltration, epidural, or nerve block. Yingmei Zheng et al23 found that dexamethasone combined with dizocine could obviously shorten the onset time of intermuscular groove nerve block, prolong the duration of analgesia and obviously reduce the adverse effects such as nausea and vomiting. 24 however, Wang Xu et al24 found that a compound small dose of dizocine was insufficient to compensate for the disadvantage of a shorter duration of analgesia caused by a low concentration of ropivacaine. Bingyanqiu et al [25] showed that the exact epidural analgesic effect of 5 mg dezocine compounded with 0. 2% ropivacaine and 100 ml normal saline was not statistically different from that of morphine ($P > 0.05$), but the adverse effect was significantly less (56. 7% in morphine group vs 6. 7% in dizocine group

In summary, dizocine can be used alone or in combination with other drugs at all stages of the perioperative period, and the analgesic effect is exact and has a certain sedative effect with few adverse effects, which is suitable for clinical promotion and application, but the dosage, mode of administration, and drug compatibility at each stage need further refinement research, and in addition, relative to special populations (such as advanced age, infants, and those with hepatic and renal dysfunction) still needs further study.

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浅谈地佐辛在围手术期的应用

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【摘要】总结探讨地佐辛在围术期的应用。

【关键词】地佐辛；围手术期；应用

地佐辛作为新型阿片受体激动拮抗药，完全激动κ受体，部分激动μ受体，不产生典型的μ受体依赖，对δ受体也有一定的激动作用。因其镇痛效果强，依赖性差，副反应小，在围手术期的应用越来越受到重视，现综述如下。

1 地佐辛的作用机制及药物代谢动力学

地佐辛为强效阿片类药物，其镇痛强度、起效时间和作用持续时间与吗啡相当。当稳态血药浓度超过 5～9ng/ml 时可缓解术后疼痛，但平均峰浓度达到 45ng/ml 时会出现不良反应；本品注射后可快速完全吸收，肌注 10mg 达峰时间为 10～90min，平均血药浓度为 19ng/ml (10～38ng/ml)。5min 内静注 10mg，平均终末半衰期 2.4h (1.2～7. 4h)，平均分布体积为 10. 1L/kg (4. 7～20. 1L/kg)，平均全身清除率为 3.

3L/hr/kg (1.7～7. 2L/hr/kg)。

2 地佐辛在全麻中的应用

2.1 诱导期

地佐辛在全麻诱导期使用可以抑制气管插管引起的咽喉、心血管反射等不良应激反应[1]，维持循环稳定及预防芬太尼和舒芬太尼引起的呛咳反应[2-3]，具体机制可能与以下因素相关[4-6]①地佐辛作用于支气管的 c 受体对抗舒太尼对气管平滑肌产生收缩效应；②减少组胺的释放来抑制呛咳反应；③竞争性阻止苏芬太尼与阿片受体的结合；④激动 K 受体产生的效应，抑制芬太尼对μ受体的激动效应，抑制呛咳反应。蒋桂琼等[7]研究显示全麻患者在气管插管时，静脉注射地佐辛（0．2 mg／kg）比静脉注射芬太尼（3μg／kg），更能有效抑制全麻气管插管的应激反应，维持循环状况稳定，这可能与地佐辛激动μ受体、拮抗κ受体，并抑制 PNE 和 5-羟色胺的重吸收，减少交感肾上腺素系统反射有关[8]。李国利[9]等研究显示 0．2 mg／kg 地佐辛用于健忘镇痛慢诱导麻醉抑制气管插管应激反应优于 2μg／kg 芬太尼，且镇静评分适当，不良反应发生率低。

2.2拔管期

地佐辛可明显降低全麻拔管期的心血管恶性反应和苏醒期躁动。于向鸿[10]等在腹腔镜胆囊手术结束前30分钟分别静脉注射不同剂量地佐辛，结果提示，静脉注射0．1 mg／kg地佐辛可以在停止全麻药后瑞芬太尼镇痛效果消失前发挥最大的镇痛效果，同时避免了手术结束后因疼痛刺激所产生的应激反应，减少全麻苏醒期不良反应的发生率，不影响呼吸及循环指标。丁翠青[11]等研究证实全麻诱导前超前使用0．07 mg／kg地佐辛可明显减少术后躁动的发生，并可降低术后BP及HR等心血管反应，同时可显著缓解患者术后的疼痛，明显地降低患者术后的不良反应。另外，不同的给药方式也影响地佐辛对全麻术后不良反应的作用。邵涛[12]等以瑞芬太尼复合麻醉下的腹腔镜胆囊手术患者为研究对象，分别于手术结束前30 min给予地佐辛0．2 mg／kg肌肉注射或静脉注射，发现在手术结束前30 min肌注地佐辛，能有效减轻瑞芬太尼复合麻醉患者痛觉过敏反应，缩短苏醒及拔管时间，提高术后镇痛镇静效果，且具有良好的安全性。儿科方面，章艳君[13]等观察发现术前静脉推注0．05mg／kg和0．1mg／kg地佐辛组均可有效减少小儿七氟烷复合麻醉苏醒期躁动，但是静脉推注0．05mg／kg地佐辛可有效减少小儿七氟烷复合麻醉苏醒期躁动且镇静强度适当，不延长术后停留时间。

3椎管内麻醉中的应用

椎管内麻醉患者处于清醒状态，麻醉本身的不适，术中的牵拉反应及患者的对手术的恐惧等导致患者紧张焦虑，甚至有频死感，很不利于手术的顺利进行，因此辅助用药必不可少，地佐辛作为新型的阿片类受体激动-拮抗药也不断被尝试用于临床，研究显示[14]静脉注射地佐辛5 mg，10分钟后可使BIS值降低（BIS 90. 2±3. 1，P<0．05），具有镇静作用，这可能跟激动中枢κ受体有关。地佐辛5 mg复合咪唑安定2 mg，10分钟后可使BIS值降低（BIS 73. 1±2. 9，P<0．05），顺行性遗忘100%，且无明显的呼吸抑制，安全舒适性好，适用于围术期患者镇静镇痛。但由于咪达唑仑半衰期短，作用时间短暂，本研究中发现，单次注射后30 min左右患者就会苏醒，BIS＞90，间断给药可使患者重新入睡，但血药浓度波动大，血流动力学影响大，且不能完全确保消除患者术中不良记忆，故地佐辛单次注射复合咪达唑仑可能是一个更理想的方法。陈晶辉[15]等研究发现：地佐辛单次药物使用剂量应该尽可能小于0. 2 mg/kg，该剂量对于患者的呼吸功能的抑制作用相对比较弱，并且不会影响麻醉平面，从而能够达到预期的麻醉效

果。

4神经阻滞中的应用

神经阻滞因其阻滞范围小，对机体的干扰小，围术期管理方便的特点，被广泛应用于四肢或体表病变局限的手术中，但也正是因为这个特点，术中经常有阻滞不全的现象发生，地佐辛可加强其麻醉效果．沈宝魁[16]研究发现小量的地佐辛加入局麻药进行臂丛神经阻滞可明显加快麻醉起效时间，延长阻滞时间，提高麻醉成功率．另外，王福朝[17]等对地佐辛的不同给药方式进行临床观察发现地佐辛局部辅助麻醉的给药方式优于静脉注射辅助用药应用于神经阻滞麻醉，这可能与其作用于外周系统的阿片受体有关．

5日间手术中的应用

近年来日间手术麻醉多用丙泊酚或七氟烷等配合阿片类药物（芬太尼或舒芬太尼等）完成，但术中易出现呼吸抑制、恶心、呕吐等副反应。目前认为低剂量静脉注射地佐辛0. 1～0. 15mg／kg配合丙泊酚或七氟烷能够安全有效的应用于无痛肠镜，输尿管镜，宫腔镜，电子纤维支气管镜及人流术等日间手术中，明显降低操作引起的心血管反应，镇痛镇静完全，苏醒迅速。

6术后镇痛中应用

地佐辛可单独用于术后镇痛. 高光伍等[18]对甲状腺癌术后患者分别静脉注射地佐辛0．1mg／kg或舒芬太尼1μg／kg进行镇痛结果提示患者术后12小时内各时间点VAS评分差异无统计学意义, 但不良反应发生率地佐辛组为26. 67%（P＞0. 05）, 舒芬太尼组为91.11%差异具有统计学意义 (P<0．05). 这与郑孝振等[19]在地佐辛对老年骨科手术患者术后镇痛研究和刘震等[20]对地佐辛在小儿耳鼻喉术后静脉镇痛的研究结果一致. 同时也有研究[21]分别将0. 80 mg／kg地佐辛与0. 01mg／kg芬太尼应用于妇科恶性肿瘤患者术后静脉自控镇痛中, 结果发现，其镇痛效果和抑制术后应激反应优于芬太尼组；且在一定程度上有保护机体的免役功能的作用，提示与芬太尼相比地佐辛更适合于妇科恶性肿瘤患者术后镇痛. 另外, 刘礼胜等[22]研究指出：与芬太尼比较地佐辛镇痛对老年患者的认知功能影响小, 术后恢复快, 原因可能是由于地佐辛没有芬太尼的二次分布作用, 药物消除半衰期较芬太尼明显缩短, 加快了药物在体内的代谢, 从而改善了术后认知功能。

地佐辛可联合阿片类药、非甾类抗炎药、右美托嘧啶等脉注射或术后静脉自控镇痛可减少纯μ受体阿片激动剂用量, 减轻头晕、嗜睡、恶心、呕吐等副反应发生, 加强镇静效果, 加强非甾类抗炎药的的镇痛效果，有效抑制术后寒战. 也可与地塞米松、罗哌卡因等联合应用于局部浸润、硬膜外或神经阻滞术后自控镇痛。郑颖梅等[23]研究发现地塞米松复合地佐辛可明显缩短肌间沟神经阻滞起效时间, 延长镇痛持续时间, 恶心呕吐等不良反应明显降低. 但王旭等[24]发现复合小剂量的地佐辛不足以弥补罗哌卡因浓度偏低带来的镇痛持续时间偏短的缺点。邴彦秋[25]等研究显示5mg地佐辛复合0. 2%罗哌卡因与生理盐水共100ml进行硬膜外镇痛效果确切与吗啡相比无统计学差异（P＞0. 05）, 但不良反应明显减少 (吗啡组56. 7%, 地佐辛组6. 7%)差异有统计学意义（P＜0. 05）

综上所述, 地佐辛可单独或复合其他药物应用于围术期的各个阶段, 镇痛效果确切且有一定的镇静作用, 不良反应少, 适合于临床推广应用, 但各个阶段的给药剂量, 给药方式及药物配伍需进一步细化研究，另外相对于特殊人群 (如高龄、婴幼儿、肝肾功能障碍者)仍需进一步深化研究.

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