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REVIEW ARTICLE

Dezocine as a potent analgesic: overview of its pharmacological characterization

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Dezocine, a synthetic opioid, introduced in 1970s as an analgesic, was redeveloped for relieving moderate to severe pain by Yangtze River Pharmaceutical Group in China in 2009. To date, dezocine occupies 45% of China's opioid analgesic market. Along with dezocine being a dominated painkiller, a certain amount of research was conducted to elucidate dezocine's action. In this review we summarize the current knowledge on the receptor, preclinical and clinical pharmacology of dezocine. Briefly, preclinical data show that dezocine is effective under varying pain conditions, particularly chronic neuropathic pain and cancer pain, through activation of opioid receptors, and inhibition of norepinephrine reuptake. Clinical data establish the effectiveness of dezocine either as a primary analgesic for postoperative pain management or a supplement for balanced analgesia. The receptor profile of dezocine is different from known pure μ agonists, and allows it to be used in combination with other opioids for additivity in efficacy or lower incidence of adverse effects.

Keywords: dezocine; opioid receptors; norepinephrine; serotonin transporter; postoperative pain; anesthesia

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INTRODUCTION

Acute pain is short-term pain that usually starts suddenly and caused by a possible tissue injury. Chronic pain typically lasts for more than 6 months and is often associated with physical or a combination of physical and mental causes, and the pain continues even after the physical injury has healed [1, 2]. Today, for treatment of acute and moderate to severe chronic pain, opioids are the most commonly used prescribed drugs. Opioids are a class of drugs naturally derived from opium poppy plant, including legally prescription pain relievers morphine, oxycodone, hydrocodone, etc., synthetic opioids fentanyl, tramadol, carfentanil, etc., and illegally heroin. The most of the prescription pain relievers are agonists targeting μ receptors. These opioid drugs produce potent analgesia, but also are highly addictive and can cause respiratory depression and even death [3, 4]. The abuse of these opioids leads to a serious national crisis that presents a significant and ongoing public health burden, is now generally known as the opioid epidemic [5]. It was reported that opioid overdose caused deaths increased nearly ten-fold [6]. Compared with pure full agonists, partial agonists or mixed agonists-antagonists may not be entirely devoid of abuse potential and respiratory depression, but definitely cause less adverse effects. As a well-known mixed agonist-antagonist, dezocine currently is the top 1 painkiller in China, and the sales reaches more than $573 million nationally. It is widely used for postoperative pain and chronic pain management.

Dezocine was redeveloped by Yangtze River Pharmaceutical Group in China and offered as a prescribed analgesic for management of postoperative pain since 2009. The opioid activity and the analgesic effects of dezocine were reviewed previously, with its pharmacokinetic properties and therapeutic trials studies [7]. Marlis' work was a landmark article, which introduced the pharmacology of dezocine (Wy-16225) and referred dezocine to be a mixed agonist/antagonist with potent analgesic effects. The agonist activity was based on the fact that dezocine produced analgesic effects in the rodent acute pain model [8], and dezocine-induced analgesia was inhibited by naloxone, a nonselective opioid antagonist, whereas the antagonist activity was replied on the finding that dezocine dose-related inhibited morphine-induced loss of righting reflex in rats. As dezocine is marketed in China and becomes dominated, more groups reinvestigate the pharmacodynamic properties of dezocine, which greatly increase the understanding of the basic principle of how dezocine works. Thus, it is critical to have a complete understanding of dezocine pharmacology in order to make well-informed prescribing and therapeutic decisions. This paper is a review of the current stage of knowledge on pharmacology and mechanism of action of dezocine.

BASIC PHARMACOLOGY

The binding affinities, selectivity, and efficacy of dezocine (Fig. 1) were investigated by in vitro laboratory assays. By using radioligand binding study, Liu et al. did a binding screen for dezocine on variety receptors and transporter proteins and reported that dezocine had K_i values of 3.7 ± 0.7 nM for μ receptors, 31.9 ± 1.9 nM for κ receptors and 527 ± 70 nM for δ receptors [9]. Dezocine's affinity with μ receptor was ~8 times for κ receptors, 142 times for δ receptors. Increasing evidence also supports that dezocine displays preferential binding to μ receptors than κ and δ

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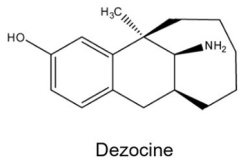
receptors [10–13]. These findings were further confirmed recently by Wang et al. showing that dezocine had K_i values of 1.46 ± 0.10 nM for μ receptors, 22.01 ± 1.52 nM for κ receptors and 398.6 ± 43.25 nM for δ receptors, respectively [14]. Thus, the data from different groups seem consistently supporting that dezocine exhibits higher affinity to μ and κ receptors over δ receptors (Table 1).

However, the intrinsic activity of dezocine seems inconsistent (Table 2). Gharagozlou with colleagues characterized the intrinsic activities of dezocine at different opioid receptors, and reported that dezocine showed agonism at both μ and δ receptors exhibiting inhibitory effect on forskolin-stimulated cAMP production. They also found that dezocine exhibited antagonism at κ receptor, since dezocine was able to antagonize the inhibitory effect of etorphine. Thus, dezocine was classified as a μ agonist, κ antagonist and δ agonist [11–13]. Dezocine's κ antagonist activity was confirmed by Liu et al. by functional [^{35}S]GTPγS binding assay [9]. Liu reported that dezocine did not stimulate κ receptor-mediated G-protein activation when used alone, but was able to inhibit full κ agonist nalbuphine and salvinorin A-induced G-protein activation. However, based on the same assay, Wang et al. evaluated the efficacy and potency of dezocine and reported that dezocine exhibited partial agonist activities at both the κ and μ receptors, with 33%–45% of the maximal stimulation obtained with full κ agonist U50,488H and μ agonist DAMGO. Moreover, dezocine exhibited inhibitory effects on U50,488H and DAMGO-mediated G protein activation [14]. Wang with colleagues further verified the agonist activity of dezocine by in vivo behavioral studies. They found that dezocine-produced significant antinociceptive effects evaluated by animal chemical pain model, and the antinociceptive effects were antagonized by both the κ antagonist nor-BNI and μ antagonist β-FNA, supporting that dezocine had κ and μ agonist activities. When dezocine was coadministered with U50,488H or morphine, it was capable of inhibiting both U50,488H and morphine-induced antinociception, supporting dezocine displayed antagonist activity [14].

In addition to opioid receptors, Liu et al. firstly reported that dezocine had two novel pharmacological targets norepinephrine and serotonin transporter. Dezocine inhibited the norepinephrine and serotonin transporter with p*Ki* of 6.00 ± 0.10 and 6.96 ± 0.08, respectively. In neurotransmitter assay, the pIC_{50s} at NET and SERT were 5.68 ± 0.11 and 5.86 ± 0.17, respectively [9] (Table 1).



Dezocine

Fig. 1 Chemical structure of dezocine.

ANALGESIC ACTIVITIES IN ANIMALS

The analgesic effects of dezocine have been demonstrated in a number of preclinical behavioral paradigms. The literature is reviewed here, particularly focusing on the effects of dezocine on acute and chronic pain with varying experimental conditions on behavioral outcomes [15–19]. The relevant studies are shown in Table 3.

Thermal pain

The hot plate test is a simple behavioral measurement to assess pain sensitivity, and is considered to be supraspinally controlled response [20]. It is based on the principle that when rodents are introduced onto a hot surface, they will perform paw licking or jumping to avoid the thermal stimulus. Marlis et al. reported that in the hot-plate test, dezocine-induced antinociceptive action with ED_{50} value of 0.06 (0.049–0.081) mg/kg (sc) [8]. However, Wang with colleagues found that in the hot-plate test, 7.5 mg/kg dezocine produced the maximum antinociception around 60%. Neither increasing the dosage nor changing the mode of administration (iv, sc or *po*) could increase the analgesic potency of dezocine [14].

Table 1. Competitive inhibition of opioid receptor binding and monoamine uptake by dezocine.

Targets		Assay/Radioligand	K_i(nM)/pK_i/pIC_{50}	Selectivity	Ref.
Opioid receptors	κ	[^{3}H]-U69,593	72 ± 21 nM (−NaCl)	μ > κ > δ	[10]
			94 ± 43 nM (+NaCl)		
	μ_1	[^{3}H]-DADLE + DPDPE	0.42 ± 0.1 nM (−NaCl)		
			6.2 ± 0.1 nM (+NaCl)		
	μ_2	[^{3}H]-DAGO + DSLET	9.0 ± 1.7 nM (−NaCl)		
			15.6 ± 1.8 nM (+NaCl)		
	δ	[^{3}H]-DPDPE	144 ± 50 nM (−NaCl)		
			2171 ± 158 nM (+NaCl)		
	κ	[^{3}H]-U69,593	24.5 ± 1.5 nM		[13]
	μ	[^{3}H]-DAMGO	–		[12]
	δ	[^{3}H]-DPDPE	–		[11]
	κ	Competitive binding assay	31.9 ± 1.9 nM	μ > κ > δ	[9]
	μ	Competitive binding assay	3.7 ± 0.7 nM		
	δ	Competitive binding assay	527 ± 70 nM		
	κ	[^{3}H]-U69,593	22.01 ± 1.52 nM	μ > κ > δ	[14]
	μ	[^{3}H]-DAMGO	1.46 ± 0.10 nM		
	δ	[^{3}H]-DPDPE	398.6 ± 43.25 nM		
Norepinephrine transporter		Competitive binding assay	6.00 ± 0.10		[9]
		Neurotransmitter assay	5.68 ± 0.11		
Serotonin transporter		Competitive binding assay	6.96 ± 0.08		[9]
		Neurotransmitter assay	5.86 ± 0.17		

Table 2. Functional activity of dezocine at opioid receptors.

Targets		Assay	Intrinsic activity			Ref.
			Agonist	Antagonist	Partial agonist	
Opioid receptors	κ	cAMP assay	–No measurable inhibitory effect on forskolin-stimulated cAMP	√Block the inhibitory effect of etorphine on forskolin-stimulated cAMP production.	–	[13]
		[^{35}S]GTPγS binding assay	–Fail to induce G protein activation	√Inhibit the effects of nalbuphine and salvinorin A	–	[9]
			–	–	√Partially induce G protein activation; Antagonize the effect of U50,488H	[14]
	μ	cAMP assay	√Inhibit forskolin-stimulated cAMP	–	–	[12]
		[^{35}S]GTPγS binding assay	–	–	√Partially induce G protein activation; Antagonize the effect of DAMGO	[14]
	δ	cAMP assay	√Inhibit forskolin-stimulated cAMP	–	–	[11]

Both the tail flick and tail withdrawal are well studied spinal reflex, albeit one under the control of supraspinal structures [21]. Intrathecal injection of dezocine (50 μg) can produce analgesic effect in a single injection, and analgesic tolerance does not appear until 1 week of twice daily injection. At 52 °C and 55 °C, the effect of dezocine on the tail contraction phase of mice showed a dose-dependency with ED_{50} of 0.08 (0.03–0.17) mg/kg and 0.16 (0.1–0.23) mg/kg, respectively [22]. Fischer et al. found that the water temperature is 53 °C, dezocine has a dose-dependent analgesic effect. The ED_{50} is 0.33 (0.28–0.41) mg/kg, which is 10 times that of morphine, but it does not appear when the water temperature is 56 °C. The analgesic ED_{50} of morphine at 56 °C is 7.7 (6.2–9.6) mg/kg [23]. When 125 μg of dezocine was administered twice daily, the antinociceptive effect and tolerance development were similar, as with the smaller dose. It was reported that, in the rat tail flick test, dezocine produced analgesic effects with ED_{50} values of 0.53 (0.37–0.76) mg/kg (ip), 0.12 (0.08–0.17) mg/kg (im), and 2.05 (1.71–2.45) mg/kg (po), respectively. The effect was ~7.7–13 times as potent as morphine [8]. Another study showed that dezocine in dose of 0.625–2.5 μg (it) significantly increased tail withdrawal latency for C57 mice [24]. Huang with colleagues also demonstrated that dezocine increased tail withdrawal latency within the dose range of 0.3125–1.25 μg (it) and produced highest effect around 43% [17].

Mechanical pain

Paw pressure test is used to measure pain response by observing the reaction to gradually increasing pressures on the normal or inflamed paw [25]. Marlis et al. reported that dezocine raised the threshold of both the normal (ED_{50} 1.55 mg/kg, *po*) and inflamed (ED_{50} 0.53 mg/kg, *po*) paws in the rat paw pressure test [8]. Barrett et al. found that, across the dose range of 1–100 mg/kg (ip), dezocine increased the paw pressure latency and produced maximal effect of 55% [26].

Chemical pain

The abdominal constriction test is commonly used as a basis for test of analgesic drugs [27]. After 0.6% acetic acid is injected, mice develop acute abdominal pain, which is characterized by abdominal contraction, limb tremor, hind limb extension and S-shaped body. It was reported that dezocine produced a dose-dependent antinociceptive effects, with an ED_{50} value of 0.2 (0.1–0.2) mg/kg (sc) [14].

Inflammatory pain

Formalin test is a widely used pain model induced by acute tissue injury. Injection of formalin into the hind paw of mice can induce a series of behavioral responses such as foot elevation, licking, and biting [28]. It produces a biphasic response, with phase I pain caused by a direct effect of the primary nociceptive afferent, and phase II pain caused by inflammation of the central sensitization of the spinal dorsal horn [29]. In the mice formalin test, Wang et al. found that dezocine produced significant analgesic effect in both phase I and phase II, with ED_{50} values of 0.4 (0.2–1.0) mg/kg (sc) and 0.4 (0.2–0.9) mg/kg (sc) [14]. Li et al. found that the mice pretreated with dezocine 3 mg/kg (ip) could only decrease the pain score in phase II, but not in phase I[24].

Complete Freund's Adjuvant (CFA)-induced pain CFA is another inflammatory pain model. Intra-articular injection of CFA produces localized edema [30]. Ye et al. reported that dezocine (0.4 μg/kg, sc) significantly increased the CFA-induced inflammatory pain threshold compared to a control group [19].

Capasaicin-induced sensitization is considered as a model for hyperalagesic states [31]. Barrett et al. found that subcutaneous injection of dezocine dose-dependently produced analgesic effects with ED_{50} values of 0.38 (0.29–0.49) mg/kg and 0.26 (0.18–0.38) mg/kg for male and female of F344 rats, respectively. Local tail injection of dezocine produced antinociceptive action

Table 3. Analgesic effects of dezocine and underlying action targets in animal studies.

Paradigm/model		Effective dose	Outcome	Mechanism of action	Ref.
Thermal pain	Hot plate test	ED_{50}: 0.06 (0.049–0.081) mg/kg (sc)	Prolong the latency to shook or raising paw	–	[8]
		2.5–10 mg/kg (sc)7.5–10 mg/kg (iv) 5–25 mg/kg (po)	Different administration routes produced maximal antinociception around 60%, higher dose can't increase the antinociception	–	[14]
	Tail flick test	ED_{50}: 0.12 (0.08–0.17) mg/kg (im) ED_{50}: 0.53 (0.37–0.76) mg/kg (ip) ED_{50}: 2.05 mg/kg (1.71–2.45) (*po*)	Prolong the response time to flicking tail	–	[8]
	Tail withdrawal test	0.625–2.5 μg (it)	Dose-dependently increase tail withdrawal latency	–	[24]
		0.3125–1.25 μg (it)	Prolong the tail withdrawal latency in dose-dependent manner and highest dose produces effect about 43%	–	[17]
		ED_{50}: 0.08 (0.03–0.17) mg/kg (ip) ED_{50}: 0.16 (0.1–0.23) mg/kg (ip)	Dose-dependently increase tail withdrawal latency	–	[22]
		ED_{50}: 0.33 mg/kg (0.28–0.41) (ip)	Dose-dependently increase tail withdrawal latency	–	[23]
Mechanical pain	Paw pressure test	ED_{50}: 1.55 mg/kg (*po*)	Prolong the latency to normal paw withdrawal	–	[8]
		ED_{50}: 0.53 mg/kg (*po*)	Prolong the latency to inflamed paw withdrawal		
		1–100 mg/kg (ip)	Produce dose-dependent increases in antinociception and highest dose produces effect around 55%	–	[26]
Vesical pain	Abdominal constriction test	ED_{50}: 0.2 (0.1–0.2) mg/kg (sc)	Reduce the number of abdominal constriction	κ opioid receptor activation μ opioid receptor activation	[14]
Inflammatory pain	CFA-induced pain	0.4 μg/kg (sc)	Produce mechanical antiallodynia	–	[19]
	Formalin test	Phase I ED_{50}: 0.4 (0.2–1.0) mg/kg (sc)	Reduce the time spent licking or flinching	–	[14]
		Phase II ED_{50}: 0.4 (0.2–0.9) mg/kg (sc)	Reduce the time spent licking or flinching	–	[14]
		3 mg/kg (ip)	Reduce the time spent biting and elevating the leg	–	[24]
	Capsaicin-induced hyperalgesia	male ED_{50}: 0.38 (0.29–0.49) mg/kg (sc) female ED_{50}: 0.26 (0.18–0.38) mg/kg (sc)	Produce thermal antihyperalgesia	–	[32]
		male ED_{50}: 236.7 μg (141.9–394.9) (tail) female ED_{50}: 207.7 (131.3–328.5) μg (tail)	Produce thermal antihyperalgesia	–	
Neuropathic pain	Spinal nerve ligation model	ED_{50}: 0.6 (0.1–0.3) mg/kg (sc)	Produce mechanical antiallodynia	μ opioid receptor activation Norepinephrine reuptake inhibition	[16]
		ED_{50}: 0.3 mg/kg (0.1–1.4) (sc)	Produce thermal antihyperalgesia		
	Chronic constriction injury model	3 mg/kg (ip)	Produce mechanical antiallodynia and thermal antihyperalgesia	–	[15]
	Peripheral nerve compression model	0.1 mg/kg (ip)	Produce mechanical antiallodynia	–	[33]
Cancer pain	Bone cancer pain	ED_{50}: 0.6 mg/kg (0.4–1.0) (sc)	Reduce mechanical allodynia	μ opioid receptor activation Norepinephrine reuptake inhibition	[18]

Table 4. Clinical Studies using dezocine alone.

Type of surgery	Group	Dose or method of injection	Outcomes				Ref.
			Reduce the use of anesthetics	Improve analgesia	Improve the satisfaction of patients	The incidence of side effects	
Abdominal operation	Dezocine	0.05, 0.1, 0.15 mg/kg (iv)	Yes	Yes	–	Reduce the patient's stress, and have fewer side effects	[43]
	Fentanyl	10 μg/kg (iv)					
Maxillofacial procedures	Dezocine	0.1 mg/kg (iv)	–	Yes	Yes	Reduce the incidence of sore throat	[38]
	Flurbiprofen axetil	1 mg/kg (iv)					
	Equal volume of saline	iv					
Abdominal surgery	Dezocine	0.1 mg/kg (iv)	–	–	–	Reduce the incidence of catheter-related bladder discomfort	[37]
	Flurbiprofen axetil	1 mg/kg (iv)					
Nasal endoscopic operation	Dezocine	0.1 mg/kg (im)	–	Yes	Yes	Reduce the incidence of restlessness, chills, nausea, and lethargy	[45]
	Equal volume of saline						
Gynecological laparoscopic surgery	Dezocine	0.1, 0.15, 0.2 mg/kg (iv)	Yes	–			[39]
Laparoscopic cholecystectomy	Equal volume of saline	–					[40]
	Dezocine	0.15 mg/kg	Yes	Yes	Yes	Reduce incidence of vomiting and reduce sedation	
Laparoscopic cholecystectomy	Dezocine	0.1 mg/kg (im)	Yes	Yes	–	Reduce the incidence of cough	[42]
	Equal volume of saline						
Inguinal hernia repair	Dezocine	im	–	Yes	Yes	–	[35]
	Placebo						
Open abdominal surgery	Equal volume of saline	iv					[36]
	Dezocine	0.15 mg/kg (iv)	Yes	Yes	–	–	
Radical surgery	Dezocine	0.6 mg/kg	–	No	–	Reduces the incidence of sedative	[44]
	Oxycodone	1 mg/kg					
Inguinal hernia	Ringer's lactate+dezocine	0.1 mg/kg	Yes	Yes	–	Reducing emergence agitation	[46]
	Ringer's lactate						
Laparoscopic cholecystectomy	Dezocine	0.15 mg/kg (iv)	Yes	Yes	Yes	Reduces the incidence of sedative and less nausea	[41]
	Equal volume of saline	iv					

Table 5. Clinical studies using dezocine combined with other agents.

Type of surgery	Group	Injection method	Outcomes				Ref.
			Reduce the use of anesthetics	Improve analgesia	Improve the satisfaction of patients	The incidence of side effects	
Upper abdominal surgeries or thoracotomies with general anesthesia	Butorphanol 1 mg	iv					[61]
	Dezocine 2 mg + butorphanol 0.5 mg		Yes	Yes		Reduce vomiting and reduce cognitive function	
Painless gastroscopy	Propofol 1 mg/kg	–	–	–	–	–	[70]
	Propofol 1 mg/kg + dezocine 20 μg/kg	–	–	–	–	Reducing the respiratory depression and body movement	
Indolent colonoscopy	Propofol 1.5–2.0 mg/kg + dezocine 5 mg/kg	iv	–	–	–	Reducing the nausea and vomiting	[68]
Gastroscopy and colonoscopy	Propofol 1.0–2.5 mg/kg + dezocine 0.05 mg/kg	iv	Yes	Yes	–	Shorten wake-up time, reducing the rates of hypopnea, jaw thrust, body movements	[67]
	Propofol 1.0–2.5 mg/kg + sufentanil 0.10 μg/kg	iv					
	Propofol 1.0–2.5 mg/kg + fentanyl 1.0 μg/kg	iv					
	Propofol 1.0–3.0 mg/kg + saline 2–3 mL	iv					
Open hepatectomy	Ropivacaine + saline	iv	–	–	–	Reducing the incidience of restlessness and cough	[66]
	Ropivacaine + dezocine						
Strabismus surgery	Dexmedetomidine 0.4 μg/kg	iv					[65]
	Dexmedetomidine 0.4 μg/kg + dezocine 0.1 mg/kg		-	Yes	Yes	Reducing pain and anxiety	
Hysteroscopy	Remifentanil 1.5 μg/kg + dezocine 0.03 mg/kg	iv	No	Yes	–	Reducing incidence and severity of cough	[51]
	Equal volume of 0.9% saline						
General anesthesia	Fentanyl 5 μg/kg + dezocine 0.1 mg/kg	iv	–	–	–	Reducing incidence and severity of cough	[52]
	Equal volume of 0.9% saline						
General anesthesia	Fentanyl 3 μg/kg + dezocine 0.025, 0.05, 0.1 mg/kg	iv	–	–	–	Reducing incidence and severity of cough	[53]
	Equal volume of 0.9% saline						
General anesthesia	Sufentanil 0.3 μg/kg + dezocine 0.05, 0.1 mg/kg	iv	–	–	–	Reducing incidence and severity of cough	[54]
	Equal volume of 0.9% saline						
General anesthesia	Sufentanil 0.3 μg/kg + dezocine 0.1 mg/kg	iv	–	–	–	Reducing incidence and severity of cough	[55]
	Equal volume of 0.9% saline						
General anesthesia	Sufentanil 0.5 μg/kg + dezocine 0.1 mg/kg	iv	–	–	–	Reducing incidence and severity of cough	[56]

Table 5. continued

Type of surgery	Group	Injection method	Outcomes				Ref.
			Reduce the use of anesthetics	Improve analgesia	Improve the satisfaction of patients	The incidence of side effects	
–	Equal volume of 0.9% saline	iv					[60]
	Sufentanil 2 μg/kg + metoclopramide 10 mg						
	Sufentanil 1 μg/kg + metoclopramide 10 mg + dezocine 0.1 mg/kg		–	–	Higher	–	
	Sufentanil 1 μg/kg + metoclopramide 10 mg + dezocine 0.2 mg/kg		–	–	Yes	–	
	Sufentanil 1 μg/kg + metoclopramide 10 mg + dezocine 0.3 mg/kg		–	–	Yes	–	
Thoracotomy	Morphine 1 mg/mL + dezocine 0.05 mg/mL	–	Yes	No	No	Reducing morphine requirement; reducing the incidence of postoperative nausea and pruritus	[49]
	Morphine 1 mg/mL + dezocine 0.1 mg/mL		Yes	No	No		
Colorectal cancer surgery	Sufentanil 2.3 μg/kg	iv					[59]
	Sufentanil 1.3 μg/kg + dezocine 1 mg/kg		No	No	–	Reducing the depression scores	
Gynecological laparoscopic surgery	Dezocine 5 mg/kg	iv					[47]
	Sufentanil 5 μg						
	Sufentanil 5 μg × 1/4 + dezocine 5 mg × 3/4		Yes	Yes	–	–	
	Sufentanil 5 μg × 1/2 + dezocine 5 mg × 1/2		Yes	Yes	–	–	
	Sufentanil 5 μg × 3/4 + dezocine 5 mg × 1/4		Yes	Yes	–	–	
Burn	Sufentanil 2.5 μg/kg + tropisetron 6 mg	iv					[58]
	Sufentanil 1.5 μg/kg + tropisetron 6 mg + dezocine 0.25 mg/kg		Yes	No	No	Reducing the sedative effect and nausea	
Vitrectomy	Midazolam 0.05 mg/kg	iv					[62]
	Dezocine 0.1 mg/kg		–	Yes	–	Relieve pain and anxiety, reduce nausea	
	Midazolam 0.05 mg/kg + dezocine 0.1 mg/kg		No	yes	–	Relieve pain and anxiety, reduce nausea	
	Equal volume of 0.9% saline						
Abortion	Propofol 2–2.5 mg/kg	iv					[71]
	Propofol 0.5–1.0 mg/kg + dezocine 0.1 mg/kg		–	Yes	–	Reduce sedation and respiratory inhibition	
Adiofrequency ablation	Remifentanil + dezocine	iv	–	Yes	––	Shorten wake-up time	[48]
	Remifentanil + midazolam						

Table 5. continued

Type of surgery	Group	Injection method	Outcomes				Ref.
			Reduce the use of anesthetics	Improve analgesia	Improve the satisfaction of patients	The incidence of side effects	
General anesthetic	Saline	–	–	–	–		[72]
	2% lidocaine						
	2 mg dezocine					Reduces propofol injection pain	
Surgery	Dezocine 0.1 mg/kg + etomidate 0.3 mg/kg	iv	–	–	–	Reduces the incidence of myoclonus	[64]
	Etomidate 0.3 mg/kg	iv					
Surgery	Etomidate 0.3 mg/kg	iv					[63]
	Dezocine 0.1 mg/kg + etomidate 0.3 mg/kg	iv	–	–	–	Reduces the incidence of myoclonus	

with ED_{50} values of 236.7 (141.9–394.9) μg and 207.7 (131.3–328.5) μg for male and female rats, respectively [32].

Neuropathic pain

Neuropathic pain is often presented as allodynia or hyperalgesia, caused by damage or disease affecting the somatosensory nervous system. The spinal nerve ligation (SNL) model was tightly ligating the L5 spinal nerve [16]. By using SNL model, Wang et al. found that dezocine produced time and dose-dependent mechanical and thermal analgesia, with ED_{50} values of 0.6 (0.3–1.3) mg/kg (sc) and 0.3 (0.1–0.4) mg/kg (sc), respectively [16]. Chronic constriction injury (CCI) is another commonly used neuropathic pain model, which is produced by type ligatures around the nerve. CCI causes mild compression of the nerves and leads to incomplete injury of the nerves and hyperalgesia. Wu et al. demonstrated that 3 mg/kg (ip) of dezocine can produce mechanical analgesia and thermal analgesia in CCI-induced neuralgia mice [15]. Zhang et al. used the peripheral nerve compression to build a neuralgia model, and the mechanical pain threshold was measured 21 days after the operation. It was found that intraperitoneal injection of 0.1 mg/kg dezocine significantly increased the mechanical pain threshold of the surgical model group [33].

Rat bone cancer pain

When walker 256 mammary gland carcinoma cells are injected into the tibia, mice develop behavioral signs of mechanical allodynica indicative of pain [34]. Mao et al. firstly demonstrated that dezocine produced significant mechanical analgesic effect in rat bone cancer pain model with ED_{50} value of 0.6 (0.4–1.0) mg/kg (sc) [18].

MOLECULAR MECHANISM OF ACTION

Since the new molecular targets of dezocine are identified, the molecular mechanisms underlying the antinociceptive action with dezocine treatment need to be fully understood. Recently information is garnered from preclinical studies and the findings are described in the following section.

Opioid receptors

The previous hypothesis for dezocine's mechanism of action focuses on the interaction of dezocine with opioid receptors, based on the fact that dezocine-induced analgesia was dose-related antagonized by naloxone, a nonselective opioid receptor antagonist [7, 8]. Recently, the specific receptor mediating dezocine's action was identified. By using rat neuropathic pain model, Wang et al. reported that selective μ receptors antagonist CTAP, given by intrathecal, prevented dezocine-produced mechanical antiallodynia, but κ receptors antagonist GNTI and δ receptors antagonist naltrindole did not, suggesting that dezocine produced antinociception was mediated by μ opioid receptor [16]. Wang group further applied bone pain model and confirmed the μ receptor mechanism underlying dezocine-induced mechanical antiallodynia. They reported that intrathecal injection of CTAP, not GNTI, nor-BNI or naltrindole, profoundly inhibited dezocine's mechanical antiallodynia action [18]. However, by applying different pain model, Wang et al. reported that dezocine's antinociceptive action were through both the κ and μ opioid receptors in vesical pain, since κ selective antagonist nor-BNI and μ antagonist β-FNA, given by ip, both significantly inhibited dezocine-induced antinociception. These findings suggest that dezocine produces antinociceptive action possibly via activation of κ and μ opioid receptors.

Norepinephrine reuptake

Recent reports have shown that dezocine can inhibit noradrenaline reuptake, and spinal norepinephrine was involved in pain transmission, thus, Wang et al. detected the specific effects of

norepinephrine depletory (6-OHDA) and selective α_2-adrenoceptors antagonist Yohimbe. They found that intrathecal pretreatment with 6-OHDA for 3 days depleted spinal norepinephrine, and produced inhibitory effect on dezocine-induced antinociception in SNL neuropathic pain model [16]. The dezocine's mechanical antiallydynia was also inhibited by intrathecal administration of Yohimbe. They further reported that in rat bone cancer pain model, both intrathcal administrations of 6-OHDA and yohimbe significantly reduced dezocine mechanical antiallydynia [18]. These data indicate that inhibition of norepinephrine reuptake contributes to dezocine-induced antinociception.

THERAPEUTIC TRIALS

Using dezocine alone: focus on postoperative pain control

Achieving successful treatment of postoperative pain remains to be a challenge, since poor pain control leads to prolonged hospitalization, delayed wound healing, psychological consequences and higher health care cost. Currently, dezocine is the mainstay opioids used in China for postoperative pain management. Intramuscular injection of dezocine produced effective analgesic effect and comfort in 60 patients undergoing inguinal hernia repair surgery for up to 24 h postoperatively [35]. In an open abdominal surgery, dezocine, 0.15 mg/kg intravenous given, offered significant antihyperalgesic and analgesic effect for up to 48 h postoperatively [36]. Patients intraoperatively received intravenous dezocine 0.1 mg/kg reduced the incidence and severity of postoperative catheter-related bladder discomfort compared to flurbiprofen axetil 1 mg/kg [37]. At same dosage, intravenous dezocine significantly decreased the postoperative sore throat and improved patient satisfaction after maxillofacial procedures compared to flurbiprofen axetil 1 mg/kg [38]. Zhou et al. demonstrated that preoperative 0.15 mg/kg dezocine intravenous administration effectively managed postoperative pain following laparoscopic cholecystectomy and gynecological laparoscopic surgery [39–41]. Similar results were reported by Zhu et al. that preoperative administration of intramuscular dezocine (0.1 mg/kg) was effective in reducing postoperative pain for laparoscopic cholecystectomy [42].

A few studies carried out dezocine in elderly patient undergoing abdominal operation surgery. Yao et al. reported that deozcine (0.05, 0.1, 0.15 mg/kg, iv) dose-dependently produced analgesic effects, decreased postoperative tracheal extubation-induced stress response, and reduced the occurrence rate of adverse complication, and the sedative effect of dezocine (0.05 mg/kg) was lower than that of the control group fentanyl (10 μg/kg) [43]. In cervical cancer treated with radical surgery, deocine 0.6 mg/kg was effective for postoperative analgesia, but the efficacy was lower than 1 mg/kg oxycodone [44]. Patients undergoing endoscopic sinus surgery received 0.1 mg/kg dezocine intramuscularly before the start of surgery can reduce the occurrence of restlessness, chills, nausea and lethargy [45]. In inguinal hernia, administration of dezocine 0.1 mg/kg decreased the incidence and severity of emergence agitation in preschool children [46]. The relevant clinical studies are shown in Table 4.

Studies using dezocine combined with other agents

In addition to being used alone for pain therapy, combined use of dezocine with other agents increasingly has attracted the attention with exhibiting better analgesia, anesthesia induction effects, or fewer adverse reactions, including drowsiness, vomiting, nausea, or urine retention. The relevant clinical studies are shown in Table 5.

Dezocine with opioid analgesics

When dezocine was administered in combination with sufentanil after gynecological laparoscopic surgery, the analgesic effects were improved and the consumption of sufentanil was significantly reduced [47]. In liver cancer patients undergoing radiofrequency ablation, the dezocine-remifentanil method has a better analgesic effect, and can effectively shorten wake-up time and regulate the expression of inflammatory cytokines TNF-α and IL-6 compared with midazolam-remifentanil intravenous anesthesia [48]. Wu et al. reported that the low concentration of dezocine in combination with morphine, morphine/dezocine: 1/0.05 and 1/0.1 could enhance the postoperative analgesia following thoracotomy, meanwhile, decrease nausea and pruritus [49]. However, Gal and DiFazio reported that the order of administration affected the efficacy of the combination of dezocine and morphine. Dezocine, when given to patients who had received a prior dose of morphine, produced a dramatic increment in analgesia. But with reverse sequence, no additive action was observed [50]. This phenomenon may result from dezocine's action at the κ receptor, norepinephrine and serotonin reuptake transporters.

Opioid analgesics have severe respiratory depression and cause patients to cough during general anesthesia operations. Studies show that use of dezocine combined with sufentanil, remifentanil or fentanyl can significantly improve the cough caused by opioids, but have no effect on heart rate [51–57]. For burn patient, dezocine 0.25 μg/kg and sufentanil 1.5 μg/kg can reduce the sedative effect and nausea after skin grafting [58].

Elderly patients may have greater sensitivity to opioid analgesics. Zhao et al. used 1.3 μg/kg sufentanil and 1 mg/kg dezocine in elderly patients colorectal cancer surgery, while the control group received 2.3 μg/kg sufentanil. The depression index of the patients was evaluated 48 h after the operation. The depression index of the patients in the dezocine and sufentanil group was lower than that in the sufentanil group [59]. Wang et al. found that in elderly patient postoperative patient controlled intravenous analgesia, 0.1 mg/kg dezocine + 1 μg/kg sufentanil + 10 mg metoclopramide can significantly improve patients' satisfaction [60]. Postoperative cognitive dysfunction is a severe postoperative complication that occurs in elderly patients. In a 40 elderly patient undergoing upper abdominal surgeries or thoracotomies with general anesthesia study, dezocine and butorphanol analgesia had transient effects on postoperative cognitive function, and the effect was lower than that of dezocine and butorphanol only group [61].

Deozocine with different anesthetic agents

When 0.1 mg/kg dezocine was intravenously administered in combination with 0.05 mg/kg midazolam for anesthesia before vitrectomy, improved pain relief occurred and the incidence of vomiting was reduced [62]. When 0.1 mg/kg dezocine was intravenously injected before etomidate to induce anesthesia, it effectively reduced the occurrence of intraoperative myoclonus [63, 64]. In strabismus surgery, intravenous injection of dezocine and dexmedetomidine can effectively reduce pain and anxiety [65]. In open hepatectomy, infiltration anesthesia with dezocine and ropivacaine can inhibit the secretion of pain factors, significantly shorten the anesthesia recovery time of patients, reduce postoperative body stress and cough in the experimental group and produce less side effects such as restlessness and cough [66].

In adult gastroscopy and colonoscopy, propofol was widely used to induce and maintain anesthesia after injection of dezocine. When propofol 1.0–2.5 mg/kg was used in combination with dezocine 0.05 mg/kg, sufentanil 0.10 μg/kg, and fentanyl 1.0 μg/kg, the analgesic usage and pain score of the dezocine group were significantly lower than those of other groups. With regard to postoperative recovery time, it was found that the recovery period was shorter in the dezocine group and sufentanil group [67]. Xu et al. also found that dezocine combined with propofol reduced the dosage of propofol and reduced the occurrence of side effects such as nausea and vomiting [68]. A totaling 630 patients included meta-analysis studies further confirmed that dezocine could prevent propofol injection pain and mitigate its severity [69].

In painless gastroscopy, dezocine 20 μg/kg and propofol 1 mg/kg has lower incidence rate of respiratory depression and body movement than propofol 1 mg/kg alone [70]. In painless abortion, dezocine 0.1 mg/kg combined with propofol 0.5–1.0 mg/kg can reduce postoperative tension as well [71]. Lu et al also reported that dezocine decreased propofol injection pain as effective as lidocaine [72].

Potential role for the treatment of opioid dependence

Opioids have potent analgesic effects, and are commonly used for the management of pain. However, prolonged use, misuse or use without medical supervision can lead to a dependency or addiction. Opioid medicines including methadone and buprenorphine have been used extensively for maintenance treatment of opioid dependence. Wu et al found that dezocine effectively alleviated morphine physical withdrawal syndromes and reinstatement of conditioned place preference behaviors, suggesting that dezocine may have potential in treatment of opioid dependence [73]. Indeed, dezocine and buprenorphine share some similar properties, and both are classified as μ partial agonists. Based on μ partial agonist activity, dezocine may block or displace morphine binding to μ receptor thus contributes to reduced opioid dependence. Further studies, particularly randomized clinical trials and other experiments in human are needed to define the utility of dezocine in opioid addiction.

ADVERSE EFFECTS

Respiratory depression

Several studies have been performed to directly detect the respiratory depressant effect of dezocine. With 5 healthy subjects, it was found that dezocine was 8.6 times as potent as pentazocine in its respiratory depressant over a 3 h monitoring period [74]. Gal and DiFazio further evaluated the respiratory depressant of dezocine in a common clinical doses of 0.15 mg/kg in a group of healthy volunteers. At this dosage, they found that dezocine produced significantly respiratory depression, and this effect reached its peak at 0.3 mg/kg. Dezocine's ceiling effect of respiratory depression was similar to other agonist-antagonist analgesics such as nalbuphine and nalorphine [50]. Romagnoli and Keats also demonstrated a ceiling effect for respiratory depression of dezocine in man at 30 mg/kg, and the respiratory depression by dezocine was almost completely antagonized by naloxone [75].

Constipation

Constipation is one of the most common adverse reaction of opioid agonists. Bian with colleagues detected the effect of dezocine on intestinal mobility, and made a comparison with morphine and sufentanil. They found that morphine (5, 10, 30 mg/L) and sufentanil (20, 40, 120 μg/L) dose dependently increased the contractile tension of isolated small intestine smooth muscle, but dezocine (1.7, 3.4, 10.2 mg/L) did not cause significant effects. All the opioids decreased small intestinal propulsion. They concluded that compared to morphine and sufentanyl, dezocine might cause less intestinal side effects [76].

Inhibiting human sperm motility

Whether exposure to dezocine and other opioid analgesics could affect sperm motility was investigated by Xu et al. in vitro. It was found that both dezocine and butorphanol induced sperm-immobilizing effect, whereas, fentanyl, alfentanil and sufentanil showed partial inhibitory effects [77].

CONCLUSION AND FUTURE DIRECTIONS

Based on the combination of in vitro laboratory assay and in vivo analgesic studies, Dezocine is an opioid with mixed agonist-antagonist activity at κ and μ opioid receptors and norepinephrine/serotonin transporter reuptake inhibitor (Fig. 2) with broad-spectrum analgesic properties, including acute thermal pain, persistent chemical and inflammatory pain, neuropathic pain and bone cancer pain. Dezocine analgesia depends on acting at κ and μ opioid receptor, and inhibiting norepinephrine reuptake. The question remains open whether dezocine's action is linked to its ability to inhibit serotonin transporter reuptake, and there still remains gaps in our understanding of the molecular and behavioral pharmacology of dezocine. Recent studies introducing of neuropathic pain and bone cancer pain model to detect the analgesic effect of dezocine may shed new light on the potential clinical benefits of dezcoine, although it is reported that neuropathic pain is found to be less responsive to pure μ opioid analgesics, and current guidelines do not specifically recommend use of partial agonists or mixed agonists/antagonists for cancer pain. As a partial agonist, it usually means that the maximal effect produced will be less than that of full agonist. However, studies carried out to date appear to confirm that dezocine produced more potent or equivalent analgesia than morphine in rodents, primates and humans, and there was no ceiling effect on dezocine-induced analgesia in clinical studies. The potent analgesia of dezocine should be due to its action on multiple targets rather than a single specific target. Available clinical evidence also suggests a particular value for dezocine as an anesthetic or as a supplement to balanced anesthesia for surgical procedures. Further controlled studies will also be needed to expand efficacy, improve compliance and enhance safety of dezocine or its combination partner. Limited evidence to date indicates that the primary side effects of dezocine are similar to morphine-like μ agonist (eg, respiratory depression, constipation), but the intensity of these side effects is reduced. Additional clinical studies involving larger patient populations are required to establish the incidence of adverse effects for dezocine. Animal studies have shown that dezocine acts as μ

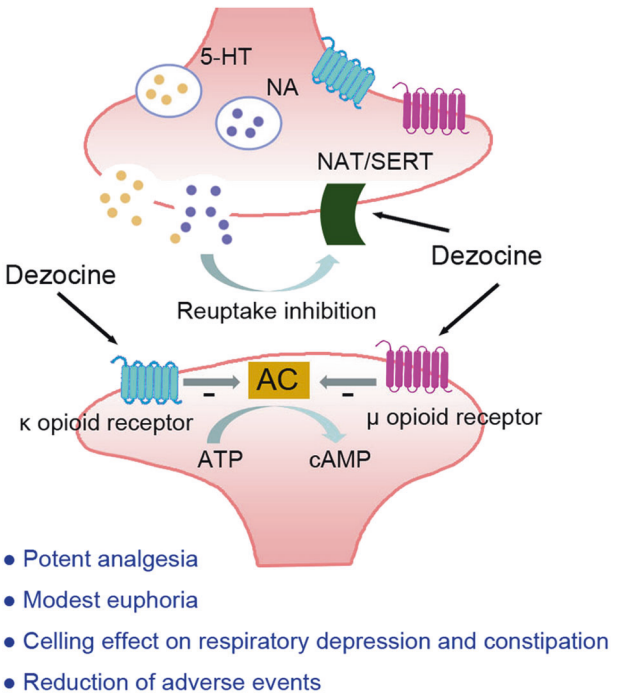


Fig. 2 Dezocine has both opioid and non-opioid mechanisms of action. It targets κ opioid receptors, μ opioid receptors, and 5-HT and NA transporters.

partial agonist. In theory, it should produce fewer abuse potential than other opioids such as morphine, heroin or fentanyl. However, since dezocine is used in China by a clinician administration, little information from controlled clinical trials is available about the abuse potential of dezocine. Studies are also needed to elucidate the abuse liability.

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ADDITIONAL INFORMATION

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