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Update on the sources, pharmacokinetics, pharmacological action, and clinical application of anisodamine

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ABSTRACT

Anisodamine is an anticholinergic drug extracted and isolated from the *Anisodus tanguticus* (Maxim.) Pascher of the Solanaceae family which is also a muscarinic receptor antagonist. Owing to the lack of natural sources of anisodamine, synthetic products are now used. Using ornithine and arginine as precursor compounds, putrescine is catalyzed by different enzymes and then undergoes a series of reactions to produce anisodamine. It has been used clinically to protect cardiac function and treat septic shock, acute pancreatitis, calculous renal colic, bronchial asthma, blood circulation disturbances, jaundice, analgesia, vertigo, acute poisoning, and other conditions.This review describes the relevant pharmacokinetic parameters. Anisodamine is poorly absorbed in the gastrointestinal tract, and it is not as effective as intravenous administration. For clinical medication, intravenous infusion should be used rather than rapid intravenous injection. With the advancement of research in recent years, the application scope of anisodamine has expanded, with significant developments and application values surging.This review systematically describes the sources, pharmacokinetics, pharmacological effects and clinical application of anisodamine, in order to provide a basis for clinical use.

1. Introduction

Anisodamine is an alkaloid originating from the roots of *Anisodus tanguticus* (Maxim.) Pascher of the Solanaceae family. The molecular structure of anisodamine is tropine-6-hydroxy-3-depinate, also known as 654, and its natural product is raceanisodamine, an M-choline receptor blocker known as 654–1[1]. Owing to the scarcity of natural products, they have been artificially synthesized for clinical use in great amounts. In 1975, two racemes containing two enantiomers were produced and dubbed 654–2[2].

Atropine, anisodamine, and scopolamine are commonly used M-choline receptor blockers. The differences between them lie mainly in their structures (Table 1). There is a β-oriented hydroxyl group at the 6th position in the alcohol part of anisodamine, which makes it more polar and more difficult for it to pass through the blood–brain barrier. The central action of anisodamine is weak and rarely causes symptoms of central excitation. Thus, while scopolamine mainly affects the nervous system[3], atropine can be utilized to relieve vagus nerve inhibition of the heart, dilate the pupils, increase intraocular pressure, excite the respiratory center, and relieve respiratory depression. Pharmacologically, since anisodamine has less pharmacological impact and fewer hazardous side effects than atropine, it is frequently used in clinical and basic research[4]. For example, anisodamine is frequently used to treat septic shock[5–7] and blood circulation obstruction[8], as well as for retinal protection[9].

In this study, we performed a literature review using the keywords “anisodamine”, “pharmacological action”, “response mechanism”, and “biosynthesis” from the PubMed, Google Academic, VIP, and China National Knowledge Infrastructure (CNKI) databases to search and collate the literature on anisodamine over the last 10 years, summarizing it for better clinical anisodamine practice.

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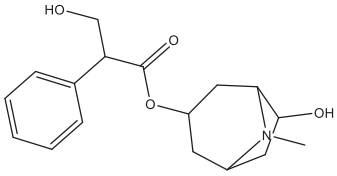
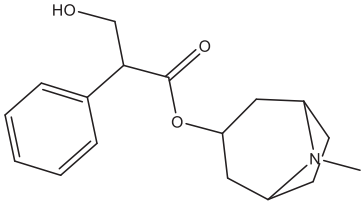
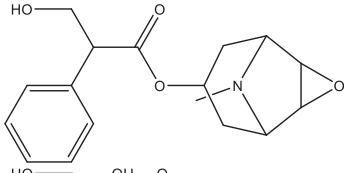
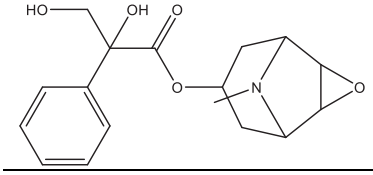
Table 1
Structure of anisodamine, atropine, anisodine, tiotropium.

Chemical structure	Name	Molecular Formula
	Anisodamine 6-hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-yl 3-hydroxy-2-phenylpropanoate	$C_{17}H_{23}NO_4$
	Scopolamine 8-methyl-8-azabicyclo[3.2.1]octan-3-yl 3-hydroxy-2-phenylpropanoate	$C_{17}H_{21}NO_4$
	Atropine 9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl 3-hydroxy-2-phenylpropanoate	$C_{17}H_{23}NO_3$
	Anisodine 9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl 2,3-dihydroxy-2-phenylpropanoate	$C_{17}H_{21}NO_5$

2. Sources

Anisodamine (6-[s]hydroxyhyoscyamine), an alkaloid first extracted from the Chinese herb *Scopolia tangutica (*Maxim). Pascher., has a structure very similar to that of atropine and is thought to be an antagonist of the M-choline acceptor. Owing to the lack of natural resources for anisodamine, artificial synthetic products are currently mostly used. The specific synthesis process is shown in Fig. 1. Anisodamine is a synthetic product with two chiral molecular centers and is currently used in clinical practice. It is a mixture of four optical isomers: A, B, C, and D. (Fig. 2).

The biosynthesis of tropinane alkaloids is initiated by ornithine and arginine. Ornithine is directly decarboxylated to putrescine in a reaction catalyzed by ornithine decarboxylase[10]. Alternatively, arginine decarboxylase converts arginine to agmatine, which is then converted to N-methylacyl putrescine by agmatine iminohydrolase and finally to putrescine by N-carbamyl putrescine aminohydrolase. The contributions of these two routes to the synthesis of downstream secondary metabolites vary between plants. For instance, arginine is mainly synthesized in *Datura* plants, whereas ornithine is the main raw material in tobacco [10–13]. Putrescine N-methyltransferase (PMT) catalyzes the N-methylation of putrescine to N-methylputrescine, which is converted to 4-aminobutylaldehyde by N-methylputrescine oxidase (MPO). PMT serves as a rate-limiting enzyme by incorporating putrescine into transanimase synthesis, which is thought to be the starting point of transanimase biosynthesis[14,15]. 4-amino-n-butanal can be spontaneously cyclized to produce the active N-methyl-Δ1-pyrrolinium cation, and plays a central role in synthesizing type III polyketide synthase (PKS) catalytic-generated 4-(1-methyl-2-pyrrolidinyl)− 3-oxo-butanoic acid. Tropinone synthase (CYP82M3) catalyzes the formation of tropinone with a tropinone ring structure, which is reduced to tropinone by tropinone reductase (TRI).

Aromatic amino acid aminotransferase (ArAT4) catalyzes the transamination of phenylalanine to produce phenylpyruvic acid, which is then reduced to phenyllactic acid by phenylpyruvic acid reductase (PPAR), providing a phenyllactamyl group for synthesis. Phenyllactic acid and uridine diphosphate (UDP)-glucose are synthesized by phenyllactic-UDP-glycosyltransferases, which produce phenyllactoglucose. Tropicin and phenyllactic acid are synthesized via esterification and condensation, respectively, to form a concholine. The conversion of the concholine into anisodamine involves molecular isomerization, a molecular rearrangement reaction. Littorine mutase (CYP80F1) catalyzes the oxidation of concholine to hyoscyamine aldehyde[16]. Hyoscylamines are generated by hyoscyamine dehydrogenase (HDH). 6β-hydroxy hyoscyamine epoxidase (H6H) is a difunctional enzyme belonging to the lysine α-ketoglutarate/iron-dependent dioxygenase family that catalyzes the hydroxylation of hyoscyamine at the C6 position to anisodamine.

3. Pharmacological Properties

3.1. Effects on treating septic shock

Septic shock is one of the oldest and most pressing problems in medicine[17]. Septic shock has a 40% mortality rate and is a major cause of morbidity and mortality in the intensive care unit (ICU); appropriate therapy should be implemented promptly to improve clinical efficacy[18,19]. Anisodamine is commonly used in clinical settings to treat several forms of shock, particularly septic shock, with fewer severe side effects than atropine[20]. In certain animal experiments, anisodamine has been demonstrated to alleviate septic shock, and additional possible therapeutic actions include suppression of thromboxane production and granulocyte and platelet aggregation[21].

In lipopolysaccharide (LPS)-induced shock, the combined administration of anisodamine and neosmine significantly reduced serum TNF- and IL-1 levels and improved survival. The combined treatment had no effect on the survival of nicotinic acetylcholine receptor (7nAChR) knockout mice, indicating that the mechanism of action is relevant to 7nAChR activation[22]. One study found that compared with the control group, the anisodamine group showed significant improvements in the extravascular lung water index (EVLWI), cardiac index (CI), intrathoracic blood volume index (ITBVI), and oxygenation index (OI) ($p < 0.05$). The mortality of the control group was 29.6%, and that of anisodamine group was 22.3%, which was significantly lower than that of the control group ($p < 0.05$). This implies that anisodamine reduces the extravascular lung water index (EVLW), improves hemodynamics, and decreases mortality in patients with early stage septic shock[23]. Particular attention should be paid to adverse cardiovascular system effects, such as coronary artery dilatation, increased coronary blood flow, tachycardia, arrhythmia induction, and primarily atrial arrhythmias, which may also induce a simultaneous increase in the ventricular fibrillation threshold[24]. For example, in a multicenter randomized trial, arrhythmias were identified in 207 shock patients (24.1%) treated with dopamine and 102 shock patients (12.4%) treated with norepinephrine ($p < 0.001$)[25]. In 2021, Yuetian et al. administered anisodamine to 181 patients in an intensive care unit, whereas 174 patients received routine nursing. ICU mortality did not differ between the two groups (22% vs. 18%; $p = 0.397$). This finding may be due to the small sample size selected for the study, which included patients with the most severe septic shock, the target group with the highest mortality rate. However, the serum lactate level was lower in the treatment group than in the usual care group on days 4–6, which supports the hypothesis that the antishock effect of anisodamine is mediated by the activation of the cholinergic anti-inflammatory pathway[26]. Some studies have shown that the antishock action of anisodamine is diminished in IL-10 mice, implying that it required the presence of IL-10. Further research revealed that IL-10 deficiency resulted in the considerable downregulation of 7nAChRs. In contrast, exogenous IL-10 receptor expression was dramatically elevated. Furthermore, anisodamine treatment amplified this upregulation. As a result, IL-10 plays a role in

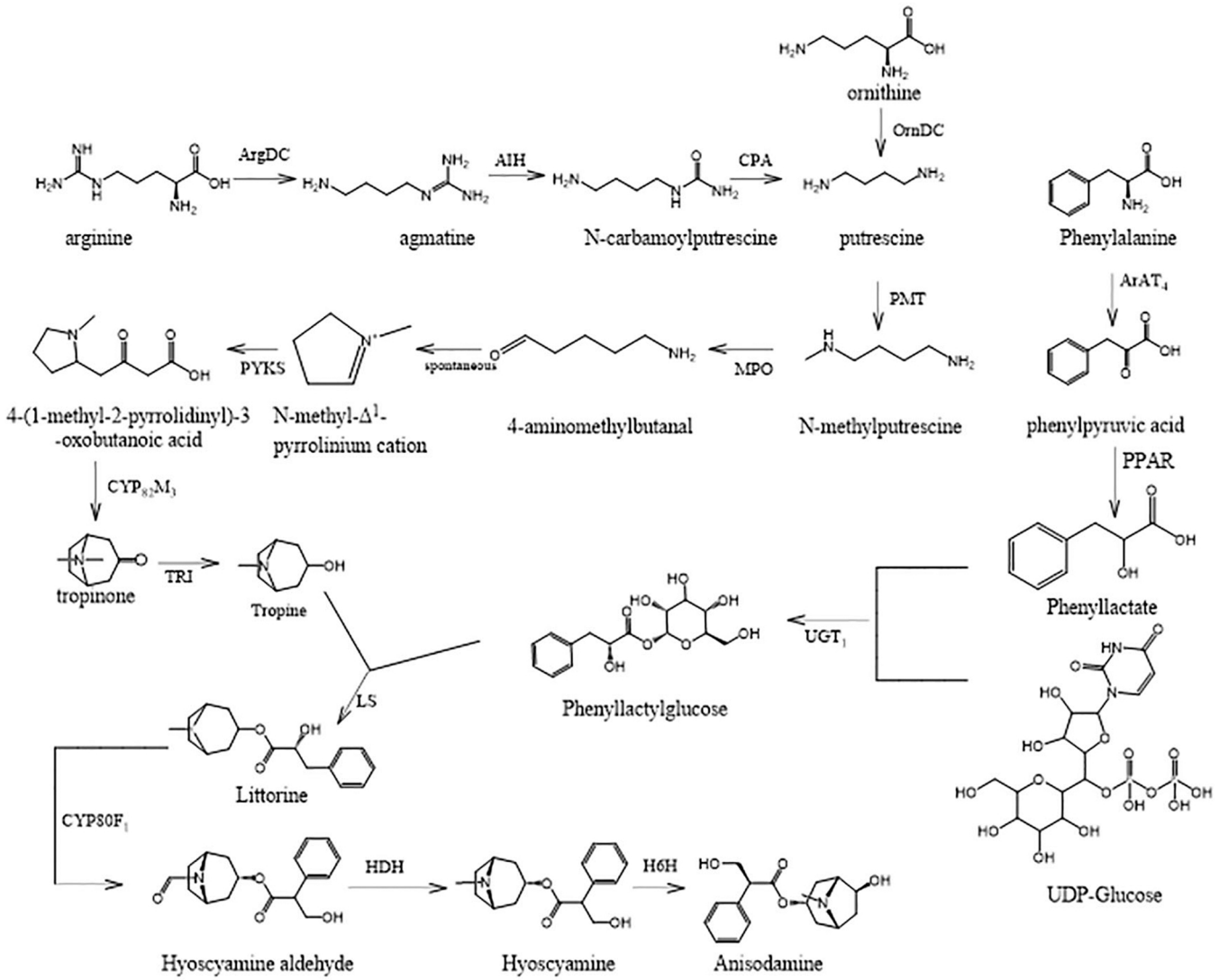


Fig. 1. The biosynthetic pathway of anisodamine.

anisodamine's antishock impact by maintaining or increasing the expression of α7nAChRs[27]. Anisodamine dilates the blood arteries, improves microcirculation, and increases the deformability of red and white blood cells in the treatment of septic shock. In addition, anisodamine reduces platelet aggregation, activation, and production of microthrombi by increasing blood flow through the capillary wall, diminishing intravascular disseminated coagulation and microthrombi, and enhancing microcirculation (Fig. 3).

3.2. Effects on liver diseases

After hepatic ischemia reperfusion, anisodamine has a protective effect against lung, kidney, and ileal injuries[28]. The analysis showed that anisodamine induced tumor cell apoptosis, whereas NLRP3 overexpression reversed the inhibitory effect of anisodamine on hepatocellular carcinoma. Notably, low NLRP3 expression enhanced the inhibitory effect of anisodamine on hepatoma xenografts in mice[29]. A pulmonary fibrosis model was established using carbon tetrachloride. The levels of matrix metalloproteinase-2, metalloproteinase-2 mRNA, and matrix metalloproteinase-2 protein in the livers of the anisodamine prevention and treatment groups significantly decreased, which inhibited liver fibrosis[30]. After biliary drainage and partial hepatectomy, the remaining liver was regenerated to 57.7% ± 7.8% of its initial total liver weight in the saline group and 68.9% ± 4.3% in the anisodamine and neostigmine groups, respectively, The Ki-67 labeling index showed 20–30% hepatocyte proliferation in the saline group and 40–50% hepatocyte proliferation in the anisodamine plus neostigmine group, in rats with cholestasis, anisodamine coupled with neostigmine can effectively reduce inflammation and enhance liver regeneration [31].

For stones with a diameter of 5 mm, the proportion of spontaneous passage was considerably higher in the anisodamine group than in the saline group (71.7% vs. 31.8%, $p < 0.05$). The proportion of patients with 5 and 10 mm stones was also substantially greater in the anisodamine group than in the control group (27.3% vs. 15.1%, $p < 0.05$). According to our findings, anisodamine expedited the spontaneous passage of a single symptomatic bile duct stone, measuring 10 mm.[32]. Certain studies have discovered that anisodamine coupled with neostigmine can also enhance liver function repair and minimize scar formation following Roux-en-Y biliary jejunostomy in rats[33]. Moreover, pethidine hydrochloride combined with anisodamine improved clinical signs and reduced the incidence of biliary cardiac reflex and discomfort in patients with advanced malignant obstructive jaundice [34].

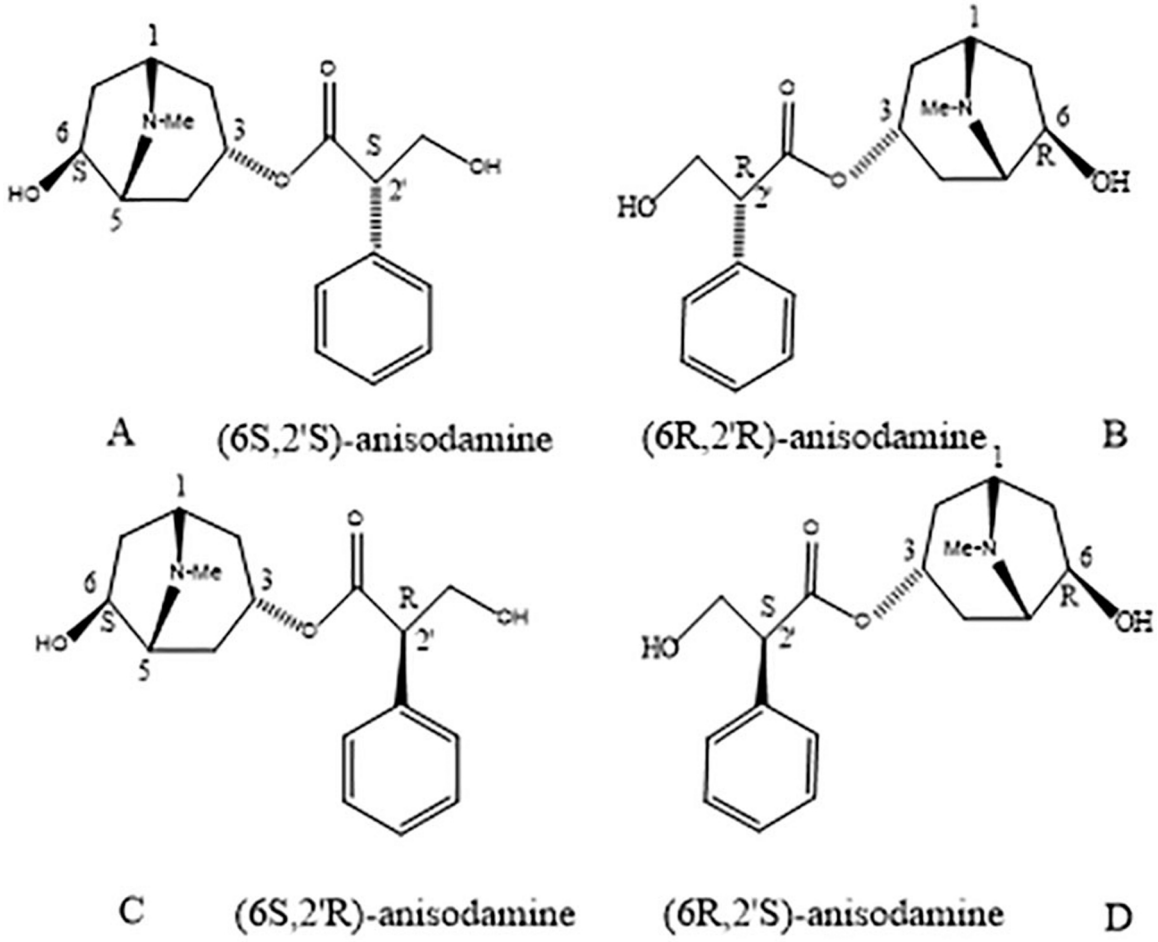


Fig. 2. The four isomers of anisodamine.

3.3. Effects on cardiac function

By reducing oxidative stress, inflammation, and apoptosis, anisodamine enhances the hemodynamic parameters of ischemia–reperfusion injury and acts as a cardiac protector[35–37]. In patients with ST segment elevation myocardial infarction (STEMI) after percutaneous coronary intervention (PCI), prophylactic intracoronary injection of anisodamine significantly enhances myocardial microcirculation perfusion and lowers major adverse cardiac events[38–43]. In anisodamine (n = 60) and placebo (n = 66) groups, at 24, 48, and 72 h after PCI, the incidence of contrast-induced nephropathy (CIN) was 5.0%, 8.3%, and 6.7% in the anisodamine group and 16.7%, 22.7%, and 19.7% in the placebo group, respectively. The incidence of CIN within 72 h of PCI was lower in the anisodamine group than in the placebo group. Anisodamine can lower the risk of CIN development after PCI.[44]. Patients who underwent myocardial infarction and took tirofiban and anisodamine together recovered their cardiac function and myocardial perfusion capacity[45].

Anisodamine and tetramethylpyrazine, two antioxidant medications, may help manage cardiac dysfunction caused by oxygen free radicals [46]. The percentages of thrombolysis in myocardial infarction 3 (TIMI 3) and survival were 11.5–92.3% and 58.1 ± 3.8% in the 2 mg anisodamine and 2 mg nicorandil groups, respectively, before and after PCI, which were higher than those in the other groups (control group: 11.5–76.9%, 51.9% ± 4.5%, anisodamine group: 7.7–84.6%, 58.6 ± 4.7%, niorandil: 7.7–80.8%, 49.3 ± 3.8%)[47]. TIMI reflects epicardial blood perfusion in patients with acute inferior myocardial infarction (AIMI) having primary PCI, and the combination of anisodamine and nicorandil significantly improves myocardial reperfusion and safeguards cardiac function.

Moreover, anisodamine shielded the myocardium from damage following cardiac arrest and resuscitation[48,49]. It also reduces acute myocardial injury caused by overtraining by suppressing the expression of caspase-1 and interleukin-18[50,51]. Patients with bradycardia can undergo enteroscopy without pain when anisodamine is administered to reduce remifentanil side effects[52]. In addition, anisodamine has been used to treat variant angina pectoris[53].

3.4. Effects on the nervous system

Because anisodamine cannot easily cross the blood–cerebrospinal fluid barrier, it has less central activity than atropine and seldom generates central excitatory symptoms. In ischemic stroke, inflammation is a persistent pathophysiological response that leads to secondary damage [54–56]. Both anisodamine and scopolamine can be used to treat motion sickness; however, anisodamine does not cause drowsiness, blurred vision, or other side effects[57]. Anisodamine combined with chlorpromazine is the most suitable drug for the treatment of intractable hiccups. The total efficacy rate was 98%, which was higher than those of the blank group and the single drugs[58]. Anisodamine has been shown to significantly reduce the expression of calcitonin gene-related peptides in the vestibular efferent nucleus and rotation-stimulated vestibular nucleus of rats, thereby treating motion sickness[59].

Medical and surgical therapy advances in recent decades have had a significant impact on ischemic stroke care. Ischemic stroke is defined as cerebral artery stenosis or occlusion, as well as cerebral blood supply insufficiency caused by brain tissue necrosis disease. A combination of neostigmine with anisodamine is used for the treatment of ischemic

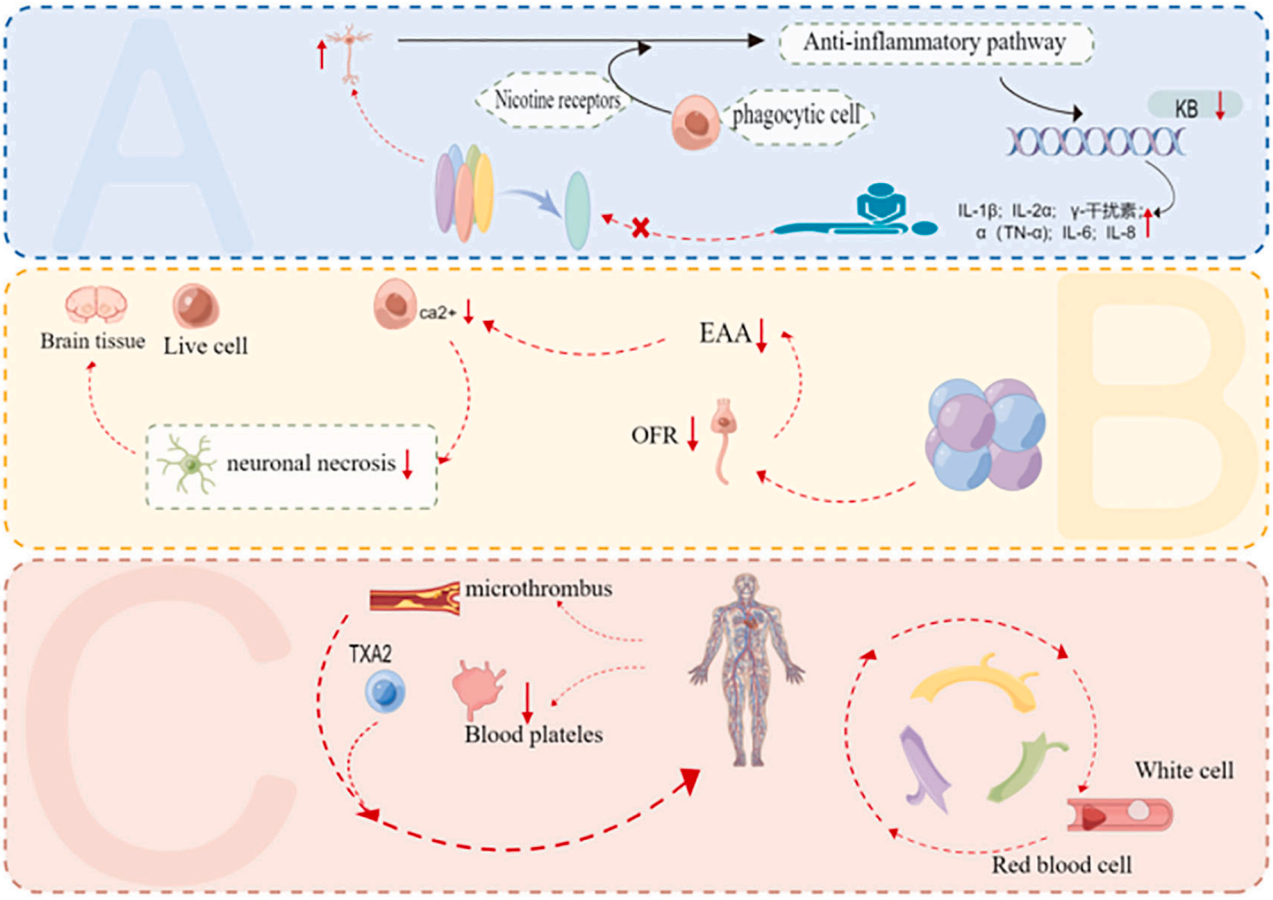


Fig. 3. Mechanism of action of anisodamine in the treatment of septic shock. (↓-low expression;↑-high expression;X:block;EAA:essential amino acid;OFR:oxygen freradical;TXA:thromboxane).

stroke. The combination had the highest protective impact at a 1:500 ratio, boosting acetylcholine binding to 7nAChRs and lowering proinflammatory cytokines[60] to 83 ± 26.48 pg/m. The PGE2 levels decreased from 493.58 ± 53.29–235 ± 30.72 pg/m. This combination can enhance the analgesic effect, reduce the incidence of adverse reactions, and is well tolerated, which has significance for clinical treatment[61]. Interestingly, in a cerebral ischemia model, Chen et al. found that the numbers of surviving neurons in the medial, middle, and lateral hippocampal CA1 region of anisodamine treated gerbils were 41% ± 12%, 50% ± 21%, and 67% ± 15% of sham-operated gerbils, respectively, which were significantly higher than those in the control group (3% ± 2%, 4% ± 3% and 7% ± 4%; $p < 0.05$), which suggested that anisodamine had an inhibitory effect on neuronal death during cerebral ischemia–reperfusion[62].

3.5. Effects on lung injury

When pulmonary fibrosis was induced by bleomycin, anisodamine alleviated endoplasmic reticulum stress.[63]. Male Sprague–Dawley rats were intraperitoneally injected with lipopolysaccharide (5 mg/kg) for 4 or 24 h after cecal ligation and puncture. After the tail vein injection of anisodamine (0, 1.8, 5.4 mg/kg) or atropine (5 mg/kg) for 24 h, the protective effect of 5.4 mg/kg anisodamine was better than that of 1.8 mg/kg and atropine[64]. This provides a basis for the clinical application of anisodamine in the treatment of lung injury. Anisodamine protected against LPS-induced acute lung injury (ALI) by suppressing LPS-stimulated changes in macrophage M1 and M2 polarization via blocking the G9a-mediated methylation of interferon regulatory factory 4 (IRF4)[65].

These findings showed that pulmonary function was significantly slowed in BLM-treated rats, which might be rescued by anisodamine. Anisodamine therapy boosts antioxidant enzyme levels, decreases the apoptotic rate and apoptosis-related proteins, and decreases fibrosis-related protein expression[66]. A massive dose of anisodamine boosted the respiratory function of individuals with traumatic LPS-induced acute lung injury (ALI) [67]. Anisodamine protected against cigarette smoke extract-induced airway smooth muscle cell proliferation and tracheal contractility[68]. These results elucidate the mechanism of anisodamine in attenuating lung injury (Fig. 4).

3.6. Effects on kidney injury

Some studies show that anisodamine protects against renal ischemia reperfusion injury in rats, and this mechanism is linked to the activation of extracellular regulated protein kinase (ERK)/p90rsk/Bad signaling [69]. A recent study found that anisodamine enhanced renal microcirculation, and that the contrast agent used in coronary angiography and angioplasty in type 2 diabetes patients with renal insufficiency was toxic to the kidneys[70,71]. Furthermore, penehyclidine hydrochloride and anisodamine alleviated hemorrhagic reperfusion and two-hit acute kidney damage caused by LPSs[72]. In addition, anisodamine hydrobromide lowered blood creatine kinase and lactic acid levels, as well as TNF-α, IL-6, and IL-1 levels in the serum and TNF-α and IL-1 levels in the renal tissue following LPS treatment, and reversed the decreased superoxide dismutase activity and increased the maximum tolerated dose content of LPS treatment[73]. As a result of suppressing LPS-induced inflammatory factors, mitochondrial dysfunction, and oxidative stress, anisodamine hydrobromide can reduce LPS-induced acute kidney

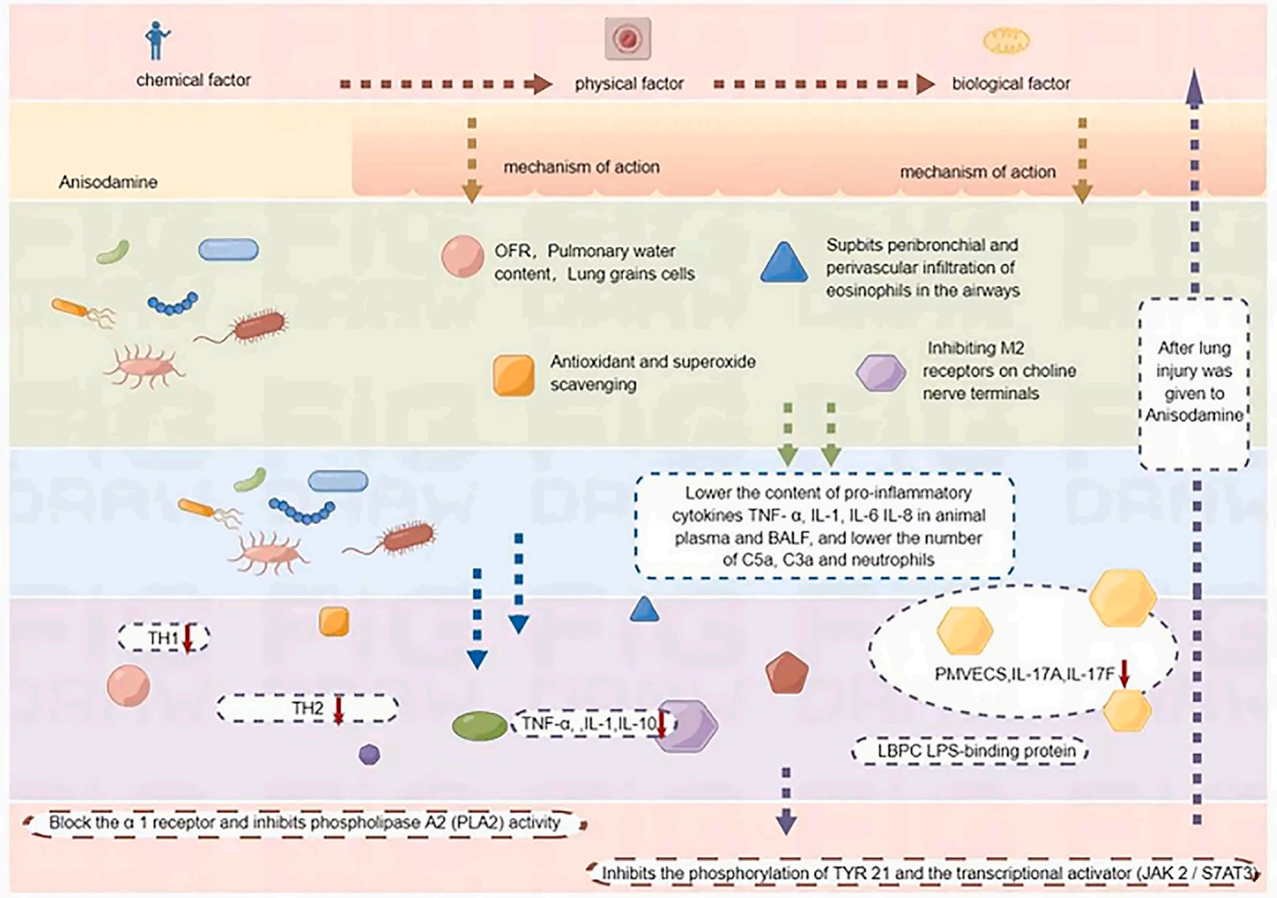


Fig. 4. Mechanism of anisodamine in attenuating lung injury. (↓-low expression;).

injury, highlighting it as a viable medication for the treatment of kidney injury in sepsis. Anisodamine can treat glycerin-induced rhabdomyolysis and kidney diseases by reducing free radicals, inflammation, and apoptosis[74,75].

3.7. Effects on microcirculation

Anisodamine significantly improves and relieves microvascular spasms and coronary microcirculation dredging[76]. After intracoronary administration of anisodamine, the systolic, diastolic, and mean pressures of the intracoronary artery increased from 115 to 123, 75–84, and 88–95 mmHg, respectively. ($p < 0.05$). In addition, the heart rate increased from 68 to 84 beats per minute ($p < 0.05$) without severe tachyarrhythmia, and the ventricular performance parameters improved significantly[77]. Anisodamine treatment reversed the injury caused by hypoxia in the microvascular system of rat brain endothelial cells[78]. Preventive intracoronary treatment with anisodamine may enhance the acute myocardial infarction survival rate with no-reflow phenomenon (NPR) by preserving the effective myocardial microcirculation status, increasing coronary perfusion pressure, and lowering the size of the myocardium[79]. Anisodamine hydrobromide protects the glycocalyx from the effects of LPSs on microvascular endothelial layer permeability and nitric oxide production[80]. Early thrombosis is the most serious risk factor for arteriovenous fistulas (AVF). The anisodamine combined with heparin treatment group had an AVF patency rate of 96.7%, the heparin therapy group had an AVF patency rate of 86.7% ($p < 0.05$), and the control group had an AVF patency rate of 83.3% ($p < 0.05$). These findings demonstrate that combining heparin and anisodamine might effectively ease the vasospasm that frequently occurs during AVF creation and lower the risk of early thrombosis[81].

Table 2
Mechanism of action of anisodamine in improving microcirculation.

Therapeutic effect	Mechanism of action	References
Stabilizing cell membrane	the fluidity of the plasma membrane↑	[83]
	phosphatidylinositol↓	[84]
	myocardial malondialdehyde↓, myocardial lipid peroxidation↓	[85,86]
	erythrocyte hemolysis ↓,LPO levels ↓	[87]
Antagonize cholinergic receptors	mAchR of vascular endothelium,NO generation↓	[88]
	nAchR↓	[89]
	arterial pressure↑, the serum levels of TNF-α and IL-1β ↓	[90]
Anticoagulation and fibrinolysis	the synthesis of thromboxane↓, the aggregation of granulocytes and platelets↓	[91]
Protect the function of vascular endothelial cells	protection of vascular endothelial glycocalyx and intercellular junctions	[80]
	protect endothelial cells, NO production↓	[82]
Direct or indirect effects on the heart	myocardial contractilit↑,venous return↑, preload ↑	[92]

↓-low expression;↑-high expression.

Table 2 shows the mechanism of action of anisodamine in improving microcirculation[82].

3.8. Effects of immunity

In children with mycoplasma pneumonia, anisodamine can boost the anti-inflammatory capacity and minimize eosinophil migration, and its

auxiliary azithromycin sequential therapy can considerably alleviate lung tissue damage and remove inflammatory cytokines[93]. Anisodamine and neostigmine dramatically lowered arthritis index, joint swelling, and weight loss. In collagen-induced arthritis (CIA) mice, combination therapy lowered the blood levels of anti-type II collagenous specific antibodies and inflammatory cytokines[94]. Several clinical trials have shown that anisodamine effectively prevented the development of infusion phlebitis[95–97]. The maximum contraction was decreased from 0.45 ± 0.0–0.28 ± 0.03 g in allergic asthmatic mice treated with anisodamine; the drug also had a strong inhibitory effect on allergen-induced bronchial hyperresponsiveness. To restore the balance of Th1/Th2 in the bronchoalveolar lavage fluid, the levels of cytokines related to Th2 cells, such as IL-4, were downregulated, and the level of cytokines related to Th1 cells, such as IFN-γ, was increased. This indicates that anisodamine controls inflammation[98].

Anisodamine prevents severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of Vero E6 cells and hindered SARS-COV-2 pseudovirus entrancing into HEK293/hACE2 cells. SARS-CoV-2 main protease was considered to be a therapeutic target for anisodamine, pointing to a potential therapy for COVID-19[99]. Jinsong et al. revealed that anisodamine hydrobromide injection can ameliorate new coronavirus pneumonia through network pharmacology-integrated molecular docking[100]. As impregnated immune adjuvants, chitosan and anisodamine not only diminished tissue damage, but also raised the protection rate following micrococcal infection[101]. Unlike the immunization method, the soaking approach did not significantly reduce the number of people required for the immunization procedure. This provides a competitive advantage because it simplifies immunization. Additionally, chitosan and anisodamine strengthened antiviral activity, restricted infectious spleen and kidney necrosis virus replication, and promoted immunological response[102]. β-glucan and anisodamine may also co-accelerate the immunological impact of *Carassius gibelio* herpes virus type 2 that inactivates vaccine immersion[103].

3.9. Effect on gastrointestinal motility

Anisodamine can be used to treat gastrointestinal motility disorders, such as acute stomach or bowel spasmodic pain[104,105]. With a success rate of 83.9%, 229 of the 582 intussusception cases that required air enema reduction in the control group were successfully repaired. Seventeen cases were successfully repaired after intramuscular injection of 654–2, with an overall success rate of 90.1%. After two attempts, reduction was successful in three cases. A 96.4% success rate was achieved overall. In children with acute intussusception, air enema before the intramuscular injection of 654–2 helps to increase the success rate of air enema reduction[106]. Combining trimebutine maleate, oryzanol, and anisodamine could significantly and more safely enhance the effectiveness of irritable bowel syndrome treatment[107].

3.10. Effects on rescue from poisoning

In one case, 35 of the 78 patients with acute alcoholism received naloxone treatment, and 43 received naloxone plus anisodamine treatment. Compared with the naloxone group, the remission and symptom disappearance times in the combination group were both significantly shorter[108]. Even at high doses of atropine, which has been used extensively to treat organophosphate (OP) toxicity, atropinization was not possible. In patients with organophosphorus poisoning who cannot be atropinized with high doses of atropine, anisodamine can shorten the atropinization process and hospital stay[109]. Additionally, anisodamine combined with blood purification slowed the progression of pulmonary fibrosis in patients with acute paraquat poisoning by downregulating the expression of matrix metalloproteinase-9 and matrix metalloproteinase 1 that enhanced the clinical therapeutic effect [110].

3.11. Effects on other pharmacological action

Anisodamine inhibited the proliferation of SKBR3 cells in the G0/G1 phase, as well as the Shiga toxin type 2-mediated production of tumor necrosis factor-α in vitro and in vivo, resulting in an anti-tumor effect [111,112]. Some studies have found that anisodamine could also be used to treat eyebrow alopecia areata[113]. Anisodamine decreases blood pressure in both normal and spontaneously hypertensive rats [114]· A study discovered that in the treatment of hypertensive diseases complicating pregnancy, anisodamine and Danshen injection combined with magnesium sulfate could successfully control blood pressure, improve plasma viscosity and urine protein, and enhance the newborn survival rate[115]. Anisodamine inhibits nuclear pulposus cell senescence and extracellular matrix degradation via the interleukin-6/Janus kinase/signal transducer and activator of transcription 3 pathway, thereby maintaining intervertebral disc tissue stability[116].

In the treatment of diabetic peripheral neuropathy, low-dose 654–2 coupled with ligustrazine is relatively safe, cost-effective, and successful [117]. The combined treatment is more effective for painful diabetic neuropathy (PDN) than anisodamine and gabapentin[118].

Oxytocin and anisodamine co-treatment can accelerate the active phase of the initial stage of labor, shorten the labor process, lower the rate of cesarean section, and enhance parturient prognosis[119]· In the flap ischemia–reperfusion injury model, the survival rate of the flap in the anisodamine group was 78.6% ± 7.3%, which was higher than that in the normal saline group[120]. Acute pancreatitis was one of the most prevalent digestive system diseases worldwide. It is an inflammatory response triggered by a variety of factors that results in the activation of the pancreatic enzymes, causing self-digestion, edema, bleeding, and even necrosis of the pancreatic tissue. Anisodamine inhibited LPS-induced apoptosis and inflammation in pancreatic acinar cells by suppressing NOD-like receptor protein 3 and inactivating the NF-κB signaling pathway[121]. Anisodamine in combination with ulinastatin may constrain the overexpression of factors in severe acute pancreatitis, reducing the severity of visceral injury[122].

4. Pharmacokinetics

Ma et al. used micellar liquid chromatography with sodium dodecyl sulfate as the surfactant, N-propyl alcohol as the modifying agent, and atropine sulfate as the internal standard to determine the in vivo plasma concentration of anisodamine. Plasma samples were immediately injected without precipitating the proteins with methyl alcohol. The pharmacokinetic characteristics of anisodamine were determined by fitting it to a one-compartment model based on extracorporeal delivery [123]. He et al. used reversed-phase high-performance liquid chromatography (HPLC) to determine the plasma concentrations and pharmacokinetic parameters of anisodamine. The method has a wide linear range with an average of 2.4% intra-day errors and 2.7% inter-day errors. Anisodamine's pharmacokinetic behavior in rabbits via gavage and intravenous injection followed the two-compartment model, and it was a rapidly distributed drug. The 50 mg/kg of anisodamine was given intravenously, and the biological half-failure times ($t_{1/2}$) of the distribution phase and elimination phase were 0.86 and 9.12 min, respectively. When anisodamine (140 mg/kg) was administered by gavage, the biological half-life ($t_{1/2}$) of the distribution phase and elimination phase were 0.45 and 4.3 h, respectively[124]. The peak area ratios (anisodamine/IS) of the plasma standards were plotted against their nominal concentrations to generate the calibration curves. The lower limit of quantification for anisodamine was determined to be 0.05 ng/mL with 94.2 accuracy and 10.9% precision, including both, which was sufficient for preclinical pharmacokinetic studies of anisodamine in beagle dogs [125].

Intravenously, atropine 1.5 mg/kg, anisodamine 8 mg/kg; anisodamine 5 mg/kg, scopolamine 1.5 mg/kg, and tiotropium 8 mg/kg were administered. The maximum plasma concentration (C_{max}) values were

274.2553.66, 267.5033.16, 340.5044.52, and 483.7578.13 ng/mL, respectively. Tiotropium had a higher C_{max} and slightly higher area under the curve. The bioavailability of atropine, anisodamine, anisodine, and scopolamine in rats was 21.62%, 10.78%, 80.45%, and 2.52%, respectively, owing to partial solubility.[126]. In different rabbits, anisodamine enantiomers exhibit nonstereoselective or stereoselective dispositions. Five rabbits were administered 140 mg/kg anisodamine hydrobromide by gavage and five rabbits were administered 50 mg/kg anisodamine hydrobromide by intravenous injection. The $t_{1/2}$ was 46–49 min (IV), 66–70 min (gavage), the clearance rate (Cl) was 33 mL/(min·kg), the apparent volume of distribution (V_d) was 1.8 L/kg, and the pharmacokinetic profile of (6 S, 2′S)- and (6 R,2′S)-anisodamine were similar in rabbits with non-stereoselective disposition. While the two remaining enantiomers had similar pharmacokinetic profiles, the $t_{1/2}$ values were 40–43 min (IV), 98–102 min (gavage), the clearance rate (Cl) was 42 mL/(min·kg), and the apparent V_d was 2.3–2.4 L/kg [127].

5. Application in Clinic

After extensive research, anisodamine has gradually been applied in clinical practice, yielding positive clinical results. In 87 patients with multiple trauma and hemorrhagic shock, the IL-6, IL-10, and TNF-a levels were lower when treated with Xuebijing combined with anisodamine than the control group [128]. Anisodamine hydrobromide effectively improved microcirculation, coronary endothelial function, blood gas indices, and cognitive function in patients with cardiac arrest and cardiopulmonary resuscitation, and the effect was significant[129]. Tan et al. discovered that a 7-d retroauricular subcutaneous injection of anisodamine combined with *G. biloba* had a considerable effect on patients with otogenic vertigo; it effectively and safely relieved the patient's condition and improved their physical and mental state[130]. After 4 weeks of treatment with anisodamine and montelukast in patients with Henoch–Schonlein purpura, Zhu et al. reported that inflammation and oxidative stress responses were significantly reduced, and the recurrence rate was low[131]. Bronchopneumonia in children is a serious and common clinical disease, and the present treatment regimen is not effective[132]. In the treatment of children with bronchial pneumonia with isodamine and terbutaline, the clinical experimental group of patients had an efficacy rate of 85.00%, whereas the traditional method of anti-infection treatment had a clinical efficacy rate of 70.00%[133].

There have been ongoing clinical trials showing the effectiveness of anisodamine in the treatment of patients with septic shock (NCT02442440). A clinical trial of anisodamine hydrobromide combined with heparin in the treatment of patients with septic shock was initiated in December 2022 to provide an alternative for the treatment of septic shock (NCT05634057). To study the treatment of postoperative nausea and vomiting with anisodamine injection at Zusanli (ST36) point (NCT05240482), patients in the placebo group will receive bilateral Zusanli (ST36) injection with normal saline (1 mL/point) and patients in the experimental group will receive bilateral Zusanli (ST36) injection with anisodamine (1 mL/points). In a comparative study of the efficacy of Buscopan® and anisodamine in the treatment of acute gastric or intestinal pain, the incidence of adverse reactions of Buscopan® was 0.65%, while no adverse reactions were observed with anisodamine (NCT01929044). The clinical trial data were obtained from a database (https://clinicaltrials.gov/).

Importantly, anisodamine was approved by the Chinese government and included in China's National Essential Medicine list in 2012[134]. Therapeutic use was determined according to information from the yaozhi database (A Chinese medical knowledge platform.https://www.yaozh.com/), anisodamine hydrobromide injection is an anticholinergic medication used primarily to treat smooth muscle spasm, gastrointestinal colic, biliary spasm, acute microcirculation disorder, and organophosphorus poisoning (Table 3).

Table 3
Important information about anisodamine used in Clinic.

Name	Anisodamine	Anisodamine Hydrobromide Injection
Contraindications	It is contraindicated in patients with hemorrhagic diseases, acute cerebral hemorrhage, glaucoma, prostatic hypertrophy, and urinary retention	Increased intracranial pressure. Use with caution in acute stage of cerebral hemorrhage and glaucoma.
Adverse reactions	The common symptoms were dry mouth, red face and blurred near vision. When the dosage is large, the heart rate can be increased, dysuria,etc. Excessive dosage may lead to central nervous systemstimulation symptoms such as convulsions and even coma.	Dry mouth, red face, mild mydriasis, blurred vision of near objects, some patients have heart rate acceleration and dysuria, most of them disappear in 1–3 h, long-term use has no accumulation of poisoning
Clinical use	It is used to relieve pain caused by gastrointestinal cramps.	It is used for toxic shock of infection, rescue of organic phosphorus pesticide poisoning, relief of smooth muscle spasm and vertigo

6. Conclusion

Anisodamine is an M-type acetylcholine receptor blocker. It can also indirectly antagonize α-adrenergic receptors, relieve vasospasm, improve microcirculation, and inhibit gland secretion and antishock.

We also discuss the strengths, weaknesses, opportunities, and threats of anisodamine (Table 4). In the first place, the benefits of anisodamine include several points. It is normally used to treat diseases, such as septic shock, smooth muscle spasms, vertigo, acute pancreatitis, calculous renal colic, and bronchial asthma[135]. Compared to atropine, fewer adverse reactions were observed. It can block acetylcholine receptors in nerve endings, thereby reducing the excitatory effect of cholinergic nerves, and is used to treat a variety of nervous system diseases and related symptoms[136]. Anisodamine can be administered by various routes such as oral administration and injection, which is convenient for patients to use and adjust the dose. In basic medical facilities, anisodamine is one of the most regularly utilized pharmaceuticals, and is an essential national medicine. However, it has the following shortcomings: in contrast to its obvious regulation of the peripheral nervous system, the pharmacological effects of anisodamine on the central nervous system are weak[137]. Anisodamine was found to be 10% less potent than atropine in eliciting excitatory electroencephalography activity in

Table 4
SWOT analysis of anisodamine.

Factors	Analysis
Strengths	1. Has been used for diseases such as septic shock, smooth muscle spasms, dizziness, acute pancreatitis 2. Less adverse reactions 3. Has been treated for neurological disorders and related symptoms. 4. Administered by multiple routes 5. One of the national Essential Medicines List
Weaknesses	1. Pharmacological effects on the central nervous system are weak 2. Caused dry mouth, blurred vision, bradycardia, dysuria and other side effects 3. Short anesthesia time
Opportunities	1. The mechanism of septic shock has remained unclear. 2. Has great potential in neurodegenerative diseases and cardiovascular diseases
Threats	1. Interactions with other drugs. 2. The mechanism of action and clinical application have needed to be further studied. 3. Lack of natural sources

unanesthetized cats and 10% less potent as a salivary stimulus[138]. Anisodamine is an anticholinergic drug that may cause many side effects such as dry mouth, blurred vision, bradycardia, and dysuria, requiring strict dose control. In addition, anisodamine can be considered a promising drug candidate. Anisodamine's major therapeutic application has been to treat septic shock, perhaps due to its capacity to enhance blood flow through the microcirculation via an unknown mechanism. In the future, anisodamine has great potential in the treatment of other diseases such as neurodegenerative diseases and cardiovascular diseases, as it may interact with other drugs. However, the development of anisodamines is currently under threat. Although anisodamine has shown efficacy in the treatment of some diseases, its therapeutic effect is uncertain, and further studies are needed to clarify its mechanism of action and clinical application. In addition, a source of anisodamine is lacking, and it is mostly used in synthetic products.

Although anisodamine has a wide range of effects and is safe, it should be used with caution in clinical practice. The benefits and drawbacks of anisodamine should be weighed against the characteristics of the disease and the patient's physical condition so that its pharmacological effects and pharmacokinetics can meet the treatment needs. Many classical clinical uses of anisodamine have been verified in many countries, thanks to the development of clinical pharmacies and in-depth research on anisodamine. New clinical uses have been gradually discovered, providing a more reliable basis for the majority of medical staff. However, large-scale randomized controlled clinical trials of anisodamine for the treatment of certain diseases are lacking.

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CRediT authorship contribution statement

This review was conceptualized by all the authors; Y.Z. conceived ideas; Y.Z. and J.Z. drafted original draft preparation; F.W., F.P. and C.P. edited the manuscript; F.W., F.P., and C.P. administrated funding; F.P. revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest Statement

The authors declared no conflicts of interest.

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