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Review Article

A REVIEW ON APPLICATIONS OF DEXMEDETOMIDINE (BXCL501) IN CNS DISORDERS

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ABSTRACT

A drug that subdues exhilaration and produces a calming effect in the subject without necessarily inducing sleep is referred to as sedative. The main system for action of these drugs is the Central Nervous System (CNS). Sedatives are slow working drugs with a levelled dose response curve. They act by modifying nerve responses in CNS to the brain which slows down brain activity thus relaxing the body. Gamma-amino-Butyric acid (GABA) is neurotransmitter which is responsible for retarding the brain functioning and sedatives increase the activity of GABA to produce more effect on the brain activity. Mostly sedatives are used to treat sleep disorders, pain or as anaesthetics. Opioids are sedatives used to treat pain, but long-term usage of these drugs leads to dependency and addiction which may be a challenge to treat. People experience withdrawal symptoms like nausea, vomiting, anxiety, insomnia and/or irritability along with seizures and loss of consciousness in some extreme cases. BXCL501 is a formulation of Dexmedetomidine used to treat agitation and symptoms of opioid withdrawal. The drug is designed in such a manner that it reduces agitation but does not produce excessive sedation. The RELEASE clinical trial of "bioxcel therapeutics" lead to the use of this drug to treat or retard opioid withdrawal symptoms and agitations. This article is aimed at reviewing and summarising existing data concerning the synthesis, chemical taxonomy, properties, mechanism of action, pharmacokinetic-pharmacodynamic profile, side effects, interactions, toxicology of dexmedetomidine.

Keywords: Dexmedetomidine, α-2 adrenergic receptor agonist, Sedative, Schizophrenia, BXCL501.

1. INTRODUCTION

Dexmedetomidine is an imidazole derivative with IUPAC name 5-[(1*S*)-1-(2,3-dimethylphenyl) ethyl]-1*H*-imidazole and molecular formula $C_{13}H_{16}N_2$. It is an active D-isomer of medetomidine which acts as a selective α-2 adrenergic receptor agonist. It also exhibits properties similar to that of an analgesic and anxiolytic drug. Dexmedetomidine was registered in 1999 in the USA for intravenous administration to the patients requiring sedation in the intensive care unit (ICU). A few years later in 2008, the use of the drug was extended to non-intubated patients before or during the surgery. Subsequently, in 2011, the European Union (EU) authorised the use of dexmedetomidine as a sedative for adult patients in the ICU to such a dose up to which a patient can be aroused easily. This exclusive property of dexmedetomidine where patients can be aroused easily along with less to no influence on the respiratory system makes it a compelling sedative in many procedures [1]. Side effects are usually related to hemodynamic alterations which may cause bradycardia, hypotension, and hypertension. Furthermore, dexmedetomidine is found to enervate stress responses during stressful events like surgery.

Precedex (Dexmedetomidine hydrochloride) is the marketed preparation of dexmedetomidine, chemically known as the S-enantiomer of medetomidine. According to IUPAC nomenclature, dexmedetomidine is (+)-4-(S)-[1-(2,3-dimethylphenyl) ethyl]-1H-imidazole monohydrochloride with molecular weight of 236.7 and molecular formula $C_{13}H_{16}N_2 \cdot HCl$. Precedex in 0.9% sodium chloride intravenous injection is an aseptic, pyrogen free solution for infusion supplied as transparent, isosmotic solution having a pH range of 4.5-7.0. Each ml contains 118mcg of dexmedetomidine hydrochloride equivalent to 100mcg of dexmedetomidine and 9mg of sodium chloride and is diluted before use [2]. The selective α-2 adrenergic agonist action is

observed in animals after a dose of 10- 300 mcg/kg. It is indicated for mechanically ventilated patients during treatment in ICU by continual infusion for not more than 24 hours. Side effects seen include hypotension, bradycardia, transient hypertension and sinus arrest. Structure of dexmedetomidine hydrochloride is depicted in Fig. 1.

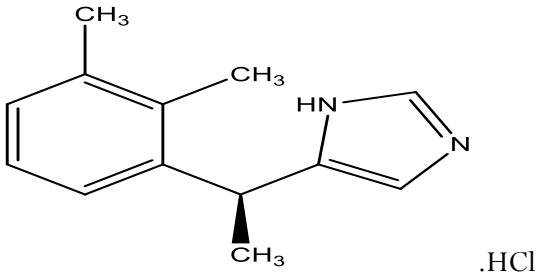

Fig. 1: Dexmedetomidine Hydrochloride

2. SYNTHESIS

The standard and most effective method for synthesis of Dexmedetomidine is as follows:

2.1. Step-I: Synthesis of Medetomidine

The authors of the most neoteric preparation of medetomidine convoluted a 9-steps synthesis with starting material as 2,3-dimethylbenzoic acid. The modification of the carboxylic acid group in 2,3-dimethylbenzoic acid brings about the formation of activated derivatives which further produce a nitro-ketone moiety. The reaction of nitro-ketone with benzylamine yields a nitro-enone which on subsequent reduction by Raney nickel gives its corresponding endiamine. A series of chemical reactions including addition-elimination-reduction via styrene derivative yields Medetomidine (13% overall yield).

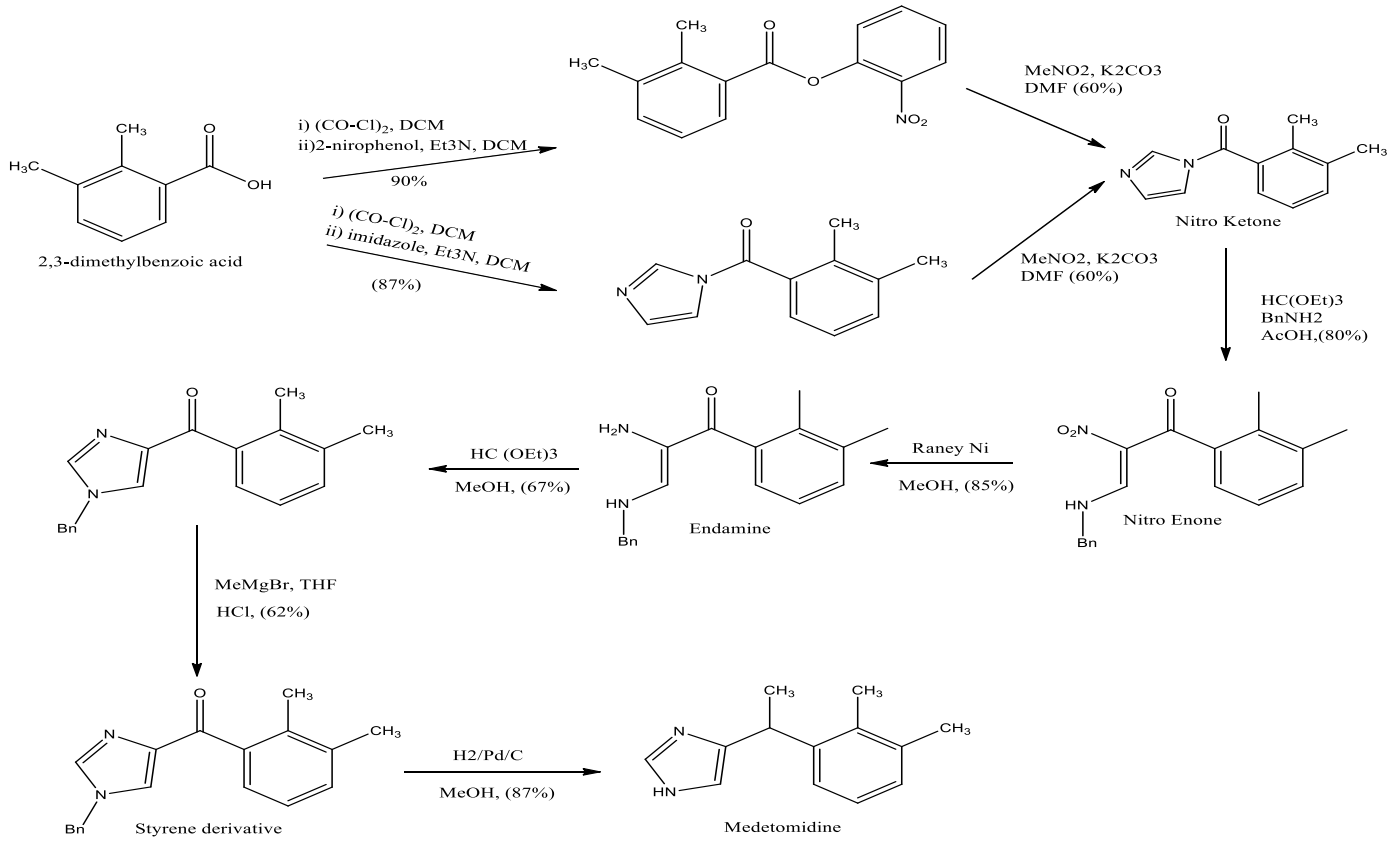

Fig. 2: Synthesis of Medetomidine

2.2. Step-II: Separation of enantiomers of Medetomidine

A. Separation of enantiomers of medetomidine was carried out by the authors (GB2206880, US4910214) using (+)-tartaric acid, followed by fractional crystallization from methanol-ethanol mixture. This repeated crystallization process aided in isolating Dexmedetomidine (17% overall yield).

B. Another method for isolating Dexmedeto-midine is reaction of medetomidine salts with (+)-tartaric acid, (-)-mandelic acid and (-)-camphor-10-sulfonic acid.

Yet the use of tartarates gives higher yield. The relative

bioactivity of the enantiomers demonstrated that the (S)-isomer is 50% more active in-vitro than the (R)-isomer of dexmedetomidine [3].

3. CHEMICAL TAXONOMY

The class of organic compounds to which dexmedetomidine belongs is o-xylenes. Structurally these are aromatic compounds containing an ortho-xylene portion, a monocyclic benzene ring with two methyl groups on the 1- and 2- positions. It is basically a compound with benzenoids and benzene substituted derivatives as the super class and class respectively. Dexmedetomidine may also contain parent groups like imidazole, azacyclic compounds and hydrocarbon derivatives [4].

4. PHYSICOCHEMICAL PROPERTIES

Dexmedetomidine is available in solid state and is highly soluble in water. It's pKa and log P parameters are 7.1 (experimental) and 2.8 (experimental),3.28 (predicted) respectively. The hydrogen acceptor count-1, hydrogen donor count-1, number of rings-2, bioavailability-1, rule of five-yes and MDDR-like rule-no are predicted using various software's like PreADMET.

5. MECHANISM OF ACTION

Dexmedetomidine is a selective α-2 adrenoceptor agonist. The release of adrenergic neurotransmitters is inhibited by α-2 adrenergic receptors. Their effect is seen on pre synaptic nerves. The stimulation of these receptors leads to a diminution in the catalytic activity of adenylyl cyclase. The activation of α receptors is associated with vasoconstriction in bronchial mucosa and dilate smooth muscles of the intestinal tract.

The mechanism of action of dexmedetomidine is distinctive and thus is different from the existing sedatives. The receptors of the brain and spinal cord, when activated, inhibit firing of neurons which gives rise to low blood pressure, decreased heart rate, sedation and analgesia. Additional areas which deviate from normal functioning involve xerostomia along with constipation-like symptoms in gastrointestinal tract and hypotony to state a few. So usually, termination of the proliferation of pain signals is observed when stimulation of α-2 adrenoreceptor hinders norepinephrine release. Heart rate and blood pressure are decreased due to inhibition of sympathetic activity by the postsynaptic activation of α-2 adrenoceptors in the central nervous system. Together these effects produce analgesia and sedation. These all effects are produced by dexmedetomidine, thus acting as a sedative and at the same time reducing the occurrence of some of the side effects from miscellaneous therapies.

Dexmedetomidine binds selectively to the pre synaptic α-2 receptors in the brain and thus inhibit norepinephrine release which further impedes postsynaptic activation of the adrenergic receptors. This causes inhibition of sympathetic activity leading to sedation. Furthermore, dexmedetomidine has also proved its efficacy as an analgesic in the spinal cord by directly stimulating the α-2 receptors which inhibit the firing of neurons [5].

6. PHARMACOKINETICS

6.1. Absorption

Currently, dexmedetomidine is only registered for IV use, yet its utility has been analysed for various routes of administration. Following IV administration, a high peak plasma level is observed which can be avoided if administered through extravascular routes. An extensive first pass metabolism is noted when it is administered through oral route giving a bioavailability of only 16% [6]. Through other routes of administration like the intranasal route or buccal mucosal route, dexmedetomidine is well absorbed and it is also suitable to deliver the drug in paediatric and/or geriatric patients [7-9].

6.2. Distribution

Dexmedetomidine is a high protein binding drug with 94% bound to albumin and orosomucoid in the plasma. The pre marketing studies demonstrated a prompt and extensive drug distribution. The preclinical studies demonstrated that dexmedetomidine freely traverses the blood brain as well as the placental barriers [10, 11]. In healthy volunteers, the half-life of the drug was found to be 6 minutes [12] whereas in ICU patients highly inconsistent values have been delineated.

6.3. Metabolism and Elimination

Liver plays a major role in the metabolism of dexmedetomidine through biotransformation. The metabolites are excreted through renal route (95%) as well as faecal route (4%).Nearly less than 1% of the drug is excreted unchanged. Around 34% of the metabolism of dexmedetomidine is due to N-glucuronidation by uridine 50-diphospho-glucuronosyl transferase. Cytochrome P450 mediated hydroxylation was illustrated in human liver microsomes [13, 14]. In healthy volunteers, an elimination $t_{1/2}$ of 2.1 to 3.1

hours [15-17] was recorded whereas 2.2 to 3.7 hours in ICU patients [18-20].

7. PHARMACODYNAMICS

7.1. Sedative Effects

Dexmedetomidine as a sedative mimics natural sleep where a person can be easily aroused. Stimulation of central pre and postsynaptic α-2 receptors in locus coeruleus leads to the soporific and hypnotic action of dexmedetomidine [21, 22]. Dexmedetomidine is preferred over other sedatives as it exhibits the characteristic of dose-dependent sedation. When a large amount of dose is given, dexmedetomidine may even cause general anaesthesia. Another advantage of using dexmedetomidine is that the cognitive functions are not critically impaired [23, 24]. In addition to this, a latest disquisition proved that dexmedetomidine reduces the time span of mechanical respiration [25]. Though the precise mechanism of dexmedetomidine is not known, it is clear that the receptors play a key role [26-29].

7.2. Analgesic Effects

The mediation of analgesic effects of α-2 agonists is presumably done by α-2 receptor binding to α-2 receptors in the central and spinal cord. The hyper-polarization of interneurons along with the reduction in release of pro-nociceptive transmitters subdues the pain transmission. When administered via the neuraxial route, dexmedetomidine displays antinociceptive effects on visceral as well as somatic pain. The prospective application of dexmedetomidine to treat and prevent neuropathic pain by a local injection produced an antiallodynic action in spinal nerve ligation-induced neuropathic pain in an animal model [30].

7.3. Cardiovascular Effects

Dexmedetomidine exhibits a typical biphasic hemodynamic response. At low and high plasma concentrations, hypotension and rise in blood pressure, respectively are observed. Administration of a single, large IV dose of dexmedetomidine, initially brings about hypertension together with bradycardia. This cardiovascular response is probably because of activation of peripheral α-2B receptors in vascular smooth muscle causing vasoconstriction; nevertheless, successive lowering of blood pressure occurs when dilation of blood vessels of central α-2A receptors is seen. A decrease in the sympathetic tone results in dose-dependent bradycardia during dexmedetomidine treatment [31, 32].

7.4. Respiratory Effects

Dexmedetomidine induces a minimal respiratory depression as compared to other sedatives, even when administered in high doses. Also, it is safe to infuse through tracheal extubation [33], in comparison to benzodiazepines or opioids. Thus, this property of dexmedetomidine proves favourable during specific conditions like awake intubation and awake craniotomy [34]. Along with this, dexmedetomidine proves beneficial during awake fiberoptic intubation. Generally, bradycardia and hypotension are observed but it can be simply taken care of with atropine and vasoactive agents [35-37].

8. SIDE EFFECTS

Most adverse events take place during or soon after a loading infusion leading to a rise or fall in blood pressure and/or lowering the heart rate which are dependent on the amount of drug as well as infusion time and frequency. For the critically ill patients, generally a slow bolus loading is preferred which in turn aids in reducing the adverse events. Though the occurrence of bradycardia is meagre, few cases of cardiac arrest associated with dexmedetomidine have been noted. The development of asystole is primarily due to factors like left anterior fascicular block, co-administration of dexmedetomidine and amiodarone. Furthermore, administration of dexmedetomidine in patients with volume depletion should be done with caution. In the end, selection of patients along with adequate dosage is foremost for secure use of dexmedetomidine [38, 39].

9. INTERACTION

Nowadays, dexmedetomidine is widely and safely used as a sedative agent as it manifests very less drug-drug interactions. Nonetheless, it has a sympatholytic effect and thus exhibits a possibility to elevate bradycardia induced by vagal stimuli. It also has the potential to change effects of other vasodilators (e.g., Nitro-glycerine- Table 1). Administration of anticholinergic agents should be contemplated to alter vagal tone [40-42]. Various drug-drug interactions are stated in the Table 1.

10. TOXICITY

As dexmedetomidine exhibits the potential to cross the placental barrier, the risk of administering it to pregnant women persists. It should only be given in such cases if its administration is beneficial as yet there have been no

clinical trials conducted in children. Hypotension, hypertension, bradycardia and hypoxia are some of the adverse effects of dexmedetomidine. An atrio-ventricular block is associated with overdose. Therefore, a monitored dosage regimen is recommended, thus reducing the risk of adverse effects.

Table 1: Dexmedetomidine- Drug interaction

Drug	Interaction
1,2-Benzodiazepine	The severity of the adverse effects may increase when administered with Dexmedetomidine
Aceclofenac/Acetylsalicylic acid/ Ampicillin/ Amphotericin B	It may decrease excretion rate of Dexmedetomidine resulting in high serum level
Albendazole/Acyclovir/ Amphetamine	Metabolism of Albendazole/Albendazole/Amphetamine may decrease when co-administered with Dexmedetomidine
Adenosine	The risk of Tachycardia may be increased when administered with Dexmedetomidine
Betaxolol	Therapeutic efficacy of Dexmedetomidine may decrease when co-administered with Dexmedetomidine
Bethanidine/ Nitroglycerine	Dexmedetomidine may decrease antihypertensive effect of Bethanidine/ Nitroglycerine
Bumetanide	Excretion rate of Bumetanide may be increased resulting in low serum level and reduction in efficacy.
Ergoloidmesylate	It can increase hypertensive and vasoconstricting effects of Dexmedetomidine.
Ipratropium	Dexmedetomidine can increase CNS depressant activity of Ipratropium
Isoprenaline	Risk of hypertension increases when it is combined with Dexmedetomidine
Levodopa	Risk of hypotension may be increased when administered with Dexmedetomidine

11. RECENT APPLICATIONS OF BXCL501

11.1. Schizophrenia

Schizophrenia is often characterised by certain episodes wherein a person is not able to differentiate between real and pseudo experiences. As the age increases, occurrence of the severe psychotic symptoms diminishes. Usually, symptoms of schizophrenia are seen at a young age and should persist for at least 6 months to draw any conclusion [43, 44].

11.2. Dementia

Certain diseases affect the memory as well as the cognitive abilities which greatly impede a person's ability to perform daily activities. All such conditions are summed under the term Dementia. Though dementia is often linked to the ageing process, it is most certainly not a usual part of ageing.

Most patients experience dementia along with behavioural and psychological problems like aggression, agitation, psychosis and depression. The condition Dementia-related psychosis (DRP) includes delusions, hallucinations along with decline in cognitive function [45, 46].

11.3. Delirium

Delirium shows symptoms alike to that of dementia but is characterised as an acute brain dysfunction where symptoms are mitigated once the causative factors are normalised. Symptoms related to the brain like disorientation, emotional dysregulation or insomnia can be noted. Other observed symptoms are reduced ability to focus or concentrate, a disturbance in awareness, memory deficit, and cognitive disturbance. Generally, delirium results from an existing physiological medical condition [47].

BXCL501 is BioXceltherapeutic's neuroscience clinical program which is being developed for treating agitation caused by schizophrenia, dementia, delirium and opioid withdrawal symptoms. BXCL501 acts as a selective adrenergic agent which can be administered through sublingual or buccal route and has proven rapid onset of action in the studies. It is the most favoured drug of choice to diminish agitation without excessive sedation. This drug product has received Breakthrough Therapy and Fast Track denomination for agitation analogous to dementia and agitation accompanying schizophrenia, dementia, bipolar disorders, respectively, by the Food

and Drug Administration (FDA).

The FDA, too, has approved filing the New Drug Application for BXCL501 in treating agitation due to schizophrenia and bipolar disorders I and II. The recent development in the year 2021, gave optimum study results for the treatment of agitation accompanying dementia, including Alzheimer's disease [48].

12. CONCLUSION

Dexmedetomidine is a successful drug used to sedate ICU patients. Its pharmacokinetic-pharmacodynamic characteristics have been examined considerably. The analgesic, sedative, cardiovascular and respiratory effects have been delineated. Further variability can be described using PK/PD models. Combining dexmedetomidine with any other sedative agent may cause respiratory depression but when used alone it is not likely to occur.

Dexmedetomidine has proved efficacious in many clinical situations. But still much more research is required to evaluate its applications. The main criteria to guarantee safe administration of dexmedetomidine is designing a proper and suitable dosage regimen which will be beneficial for the patients.

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Conflict of interest

None declared

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