

외상성 뇌손상환자에서 Amantadine의 사용

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The use of Amantadine in Traumatic Brain Injury Patients

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ABSTRACT

A variety of symptoms can occur following traumatic brain injury(TBI) or other types of acquired brain injury. These symptoms can include problems with short-term memory, attention, planning, problem solving, impulsivity, disinhibition, poor motivation, and other behavioral and cognitive deficit. These symptoms may respond to certain drugs, such as dopaminergic agents. Amantadine may protect patients from secondary neuronal damage after brain injury as a effect of NMDA receptor antagonists and may improve functioning of brain-injured patients as a dopaminergic agonist. Clinically, based on current evidence, amantadine may provide a potentially effective, safe, and inexpensive option for treating the cognitive, mood, and behavioral disorders of individuals with brain injury. The rationales for using amantadine are discussed, and pertinent literatures are reviewed.

KEY WORDS : Amantadine · Dopamine agonist · NMDA receptor antagonist · Traumatic brain injury.

서 론

외상성 뇌손상환자에서 다양한 증상이 나타날 수 있다. 이러한 증상은 단기 기억력, 주의력, 계획, 문제 해결, 충동성, 억제 장애, 동기 부족, 그리고 다른 행동 및 인지 결핍을 포함할 수 있다. 이러한 증상들은 특정 약물, 예를 들어 도파민ergic 약물들에 반응할 수 있다. Amantadine은 뇌손상 후 2차성 신경 손상으로부터 환자를 보호할 수 있으며, 도파민ergic agonist로서 뇌손상 환자의 기능을 개선할 수 있다. 임상적으로, 현재의 증거에 기반하여, Amantadine은 인지, 기분, 그리고 행동 장애를 가진 뇌손상 환자를 치료하는 데에 잠재적으로 효과적, 안전하며, 저렴한 옵션을 제공할 수 있다. Amantadine을 사용하는 이유에 대해 논의하고, 관련 문헌을 검토한다.

외상성 뇌손상(TBI) 또는 다른 형태의 획득성 뇌손상 후 다양한 증상이 나타날 수 있다. 이러한 증상에는 단기 기억력, 주의력, 계획, 문제 해결, 충동성, 억제 장애, 동기 부족, 그리고 다른 행동 및 인지 결핍이 포함될 수 있다. 이러한 증상들은 특정 약물, 예를 들어 도파민ergic 약물들에 반응할 수 있다. Amantadine은 뇌손상 후 2차성 신경 손상으로부터 환자를 보호할 수 있으며, 도파민ergic agonist로서 뇌손상 환자의 기능을 개선할 수 있다. 임상적으로, 현재의 증거에 기반하여, Amantadine은 인지, 기분, 그리고 행동 장애를 가진 뇌손상 환자를 치료하는 데에 잠재적으로 효과적, 안전하며, 저렴한 옵션을 제공할 수 있다. Amantadine을 사용하는 이유에 대해 논의하고, 관련 문헌을 검토한다.

(Thurman 1999), (1998). Vecht (1975) (dopamine metabolites) 가 Brown (1979) Levin Kraus(1994) (dopaminergic agents) (sequelae) Amantadine (dopaminergics) 가 (acute neurotransmitter alteration) , dopamine metabolite 가 (Vecht 1975 ; Pearlson Robinson 1981). amantadine NMDA(N - methyl - D - as - partate) glutamate receptor antagonist

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(excitotoxic neurotransmitter) 가 (Gianutsos 1985)
 (Weller (Allen 1983). amantadine N - methyl -
 Kornhuber 1992). , D - aspartate glutamate receptor antagonist (Riederer
 , amantadine 1991)
 , , (Weller Kornhuber
 . 1992 ; Kornhuber Weller 1997).

**Amantadine Hydrochloride의 특성과 성질
 (Characteristics and Properties of
 Amantadine Hydrochloride)**

**외상성 뇌손상 환자에서 Amantadine의 임상적인
 사용(Clinical Use of Amantadine in
 Brain-injured Patients)**

Amantadine 1954 1960 5 amantadine
 (antiviral agent) (Herr - . Gualtieri (1989)
 man 1960). Amantadine (water - soluble acid 2 144 30
 salt) . amantadine
 Amantadine G - I tract peak 가 가 19 (63%)
 plasma concentration 1~4 가 , , 가
 (half - life) 16~24 (steady state) 48 . 14 가
 72 , 5 가 . 19
 (Aoki Sitar 1988). 가 가
 (Chandler 1988 ; Bo - . (closed head injury)
 uma 1991) . , . 4
 Amantadine 3가 가 .
 ; Influenza A , 50~400mg/day , am -
 , antadine 288.3 ± 87.3mg/day .
 .
 1969 Schwab 가 Andersson (1992)
 (influenza) am - amantadine 200mg 400mg
 antadine 가 2 , ,
 amantadine anticholinergic agents (attention span),
 (Harvey 1986).
 amantadine (anticholinergic drugs) Nickels (1994) amantadine
 medication - induced movement disorder 12 . 9
 . neuroleptic - induced acute dy - 2 , 1
 stonia, medication induced postural tremor .
 (Stenson 1976 ; Borison 1983). Amantadine be - .
 nztropine (Van Putten 1987) 12 10 .
 (McEvoy 1987) 가 , ,
 가 . amantadine
 Amantadine mechanism , , ,
 dopaminergic effect 가 .
 central neuron dopamine 가 . 5 가 , pedal
 (Aoki Sitar 1988), edema, , 가
 (postsynaptic) amantadine .

amantadine
(Erkulwater Pillai 1989 ; Muller 1979 ; Roca 1990 ; Semlitsch 1992).

EEG
(higher alpha activity) (lower fast activity) 가 (slow wave activity) 가
amantadine 100mg
(vigilance) 가
(Suitsu 1992).

Moryl (1993) amantadine
multiple sclerosis Murray(1985) amantadine
Horiguchi (1990) 3 olivopontocerebellar atrophy 가 amantadine 300mg/day

Van Reekum (1995) 6 (brain injury) perseveration 가
(1999) disorientation, irrelevance, confabulation, anxiety, impulsiveness, aggressiveness, bradykinesia
amantadine 300mg/day
Barthel index 57
82 amantadine

Amantadine 사용에 대한 이론적인 근거와 작용기전(Rationale and Mechanism of Action for Using Amantadine)

1. 도파민 효현제로서의 Amantadine의 역할
 - 1) 뇌손상의 병태생리와 연관된 dopaminergic system의 역할
Vecht (1975) Van Woerkom (1977)

am - cortex striatum cortical arousal
monoamine neurotransmitter system
monoamine transmission
frontal lobe syndrome
Brown (1979)
(dopamine neurotransmission)
Graham (1987) axial brain structure (shear damage) monoamine neurotransmitter system
monoaminergic drugs
(Feeney 1982 ; Kasamatusu Pettigrew 1979 ; Kasamatusu 1981) Reiser (1988) stimulant dopaminergic drug
orbito - frontal medial temporal lobes 가 가
(Levin 1992).
2) Amantadine의 direct-indirect dopaminergic properties
Gualtieri Evans(1988)
(dopaminergic effect) psychostimulant treatment 가
1) stimulants attention deficit/hyperactivity disorder(AD/HA) inattention, distractibility, disorganization, hyperactivity, impulsiveness, emotional lability TBI(Traumatic brain injury) 가
2) stimulants hypersomnia, apathy, anergia narcolepsy, Klein - Levin syndrome, senile apathy hypoarousal 가
TBI stimulants drugs
3) stimulant attention fatigue medication AD/HA
long - term memory TBI 가
4) stimulants AD/HA perceptualmotor function, fine motor speed, accuracy stimulants TBI
5) stimulants rostral brain structure frontal neocortex dopaminergic neurotransmission

가 . fr -
 ontal lobe damage 가 TBI ;
 flexibility ,
 . 6) TBI monoaminergic transmission
 monoamine neuron pro -
 jection axial brain structure shear damage
 . Stimulants monoaminergic drugs
 `rational pharmacotherapy가
 . 7) dopamine agonist cortical recovery process
 . L - dopa coma
 . Amphetamine brain - lesioned
 rats recovery .
 Gualtieri (1989) dopamine
 presynaptic agonist methylphenidate, amphetamine,
 L - DOPA ,
 가
 (postconcussional
 syndrome) 가
 가
 L - DOPA 가
 .
 presynaptic dopamine neuron
 presynaptic dopamine agonist
 substrate가
 (Gualtieri 1989). Chandler (1988)
 direct - indirect dopamine agonist
 가 amantadine
 amantadine .
 methylphenidate L -
 DOPA bromocrip -
 tine lergotriple amantad -
 ine 가 apomorphine amphetamine
 (Allen 1983). Am -
 antadine (central neuron)
 (Aoki Sitar 1988),
 (postsynaptic)
 가 (Gianutsos 1985)
 (Allen 1983). dopamine agonist
 direct indirect profile 가 . aman -
 tadine prolactin 가
 (hypothalamic dopamine receptor)

(Siever 1981). Amantadine me -
 solimbic mesocortical dopamine system
 (striatal dopamine receptor)
 가 (Allen 1983)
 가 .
 Gualtieri (1989)
 가 amantadine
 가
 가
 amantadine 가
 ,
 cortical recovery 가
 가 (Gualtieri Evans 1988 ; Reiser 1988)
 .
 Weller Kornhuber(1992) amantadine
 (glutaminergic system) (do -
 paminergic system) 가
 neuroleptics dopamine
 neuroleptic malignant syndrome
 . amantadine NMDA
 glutamate receptor antagonist .

2. NDA 수용체 길항제로서 Amantadine의 역할

1) 뇌손상의 병태생리와 연관된 NMDA receptor antago -
 nist의 역할(The role of NMDA receptor antagonist as -
 sociated with pathophysiology of brain injury)
 (pathoph -
 ysiology)
 (primary neuronal injury) (secondary
 neuronal injury) .
 (nerve cell),
 (synapses) (cerebral blood vessel)
 가 (Bouma
 1991). 가 (pa -
 thophysiologic process) (cerebral ischemia)
 (reperfusion) (Bullock 1995).
 6 (Cottrell 1977).
 (cerebral blood flow)가
 . tissue re -
 perfusion
 (Bricolo Glick 1981). (mechanism)
 가 (lactic acid) (acidosis),
 (intracellular calcium ion) (free

radical) 가
 (1).
 (sodium - potassium pump)
 (Bullock 1995).
 (calcium) 가
 (calcium - dependent)
 (Cawley 1998). (ex -
 citatory amine) (aspartate)
 가 (Faden 1989 ;
 Cawley 1998). (glutamate)
 (aspartate) NMDA
 (Fa -
 den Salzman 1992). glutamate aspartate
 가 (Cawley
 1998). 가 glutamate
 NMDA receptor antagonist가
 (neuroprotective agent)
 glutamate
 glutamate
 (Kornhuber Weller 1997), glutamate
 receptor long - term potentiation
 (Stahl 1996). glutamate receptor antagonist

EAA(excitatory amino acid)
 glutamate
 (Kornhuber We -
 ller 1997).
 2) Amantadine의 NMDA receptor properties(NMDA re -
 ceptor properties of amantadine)
 Neuroprotective agent NMDA receptor antagonists
 phencyclidine(PCP) MK - 801
 NMDA receptor high affinity
 (Kornhuber Weller 1995). MK - 801, PCP, ket -
 amine high affinity NMDA receptor anta - gonist
 psychotomimetic side effect 가 PCP
 ketamine induced psychosis가 schizophrenic psychoses
 가 experimental phenocopy
 (Kornhuber Weller 1997). Krystal (1994)
 cognitive deficit
 PCP ketamine
 glutaminergic antagonists가
 . Alan(1999) ketamine
 NMDA - glutaminergic antagonism sites
¹⁸F - deoxyglucose PET scans pre -
 frontal cortex activation 가
 conceptual disorientation activation
 prefrontal cortex가 glutamatergic antagonism
 high aff -
 inity NMDA receptor antagonist glut -
 amate
 Kornhuber Weller(1995 ;
 1997) amantadine NMDA receptor PCP bi -
 nding site affinity가
 psych -
 otogenicity가 (2) NMDA
 receptor channel
 activity (3).
 amantadine
 (neuroprotective agent)
 (Kornhuber Weller 1997).

3) NMDA receptor antagonist와 dopamine agonist의 상
 호관계
 NMDA receptor dopamine
 Weller Kornhuber(1992) NMDA rece -
 ptor inhibition cholinergic transmission
 dopaminergic transmission

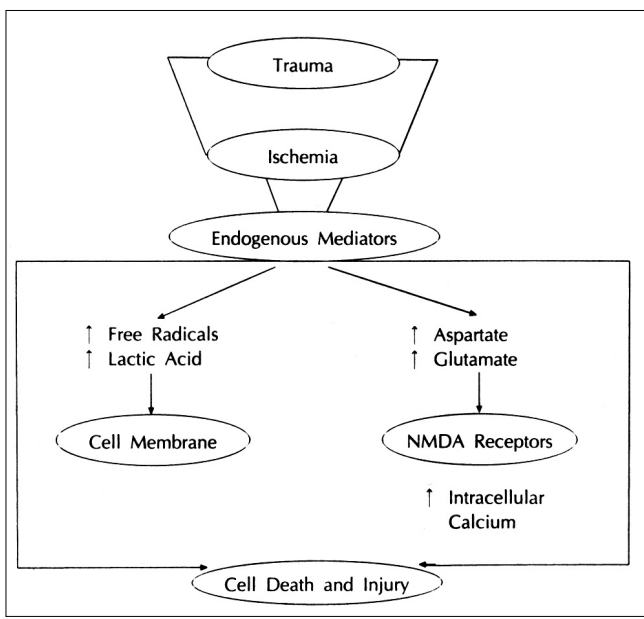


Fig. 1. Pathway of neuronal injury(Cawley et. al 1998).

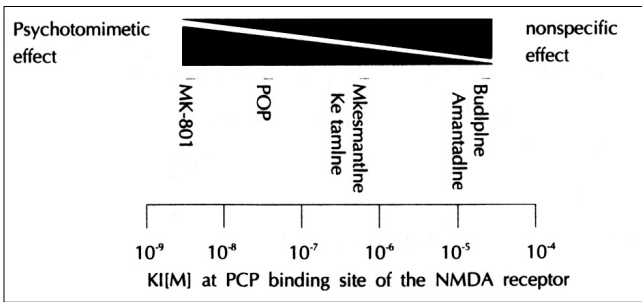


Fig. 2. High Drug affinity for the PCP binding site of the NMDA receptor is associated with psychogenicity and few Interactions with other transmitter systems(modified from [Kornhuber and Weller 1995]). The simplified graph provides Ki values for drug binding site of the NMDA receptor and seeks to illustrate how low Ki values predispose to psychotomimetic side effects but render nonspecific actions at other receptors unlikely(Kornhuber J and Weller M 1997).

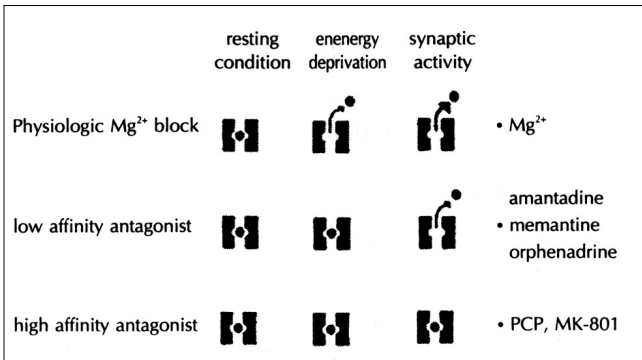


Fig. 3. Physiological and pathological NMDA receptor activity. Glutamate concentration in the synaptic cleft are higher during synaptic activity than in ischemic and hypoxia. However, glutamate elevations under pathological conditions are prolonged compared with synaptic activity and are therefore neurotoxic. Current evidence suggests that low affinity NMDA receptor antagonists may block channel activity associated with pathological conditions without interfering with physiological NMDA receptor activity(Kornhuber and Weller 1997).

NMDA receptor antagonist dopaminergic agonist
 onist가
 NMDA receptor antagonist dopaminergic agonist
 가
 Hesselink (1999) rats uncompetitive NMDA antagonist memantine prefrontal cortex dopamine dopamine metabolite DOPAC(dihydroxyphenylacetic acid) HVA(homovanillic acid) 가 가
 . Zeevalk (2000) striatum
 substantia nigra energy impairment dopamine loss NMDA receptor가 , Voll-enweider (2000) ketamine striatal dopamine D2 receptor concentration 가 NM-DA receptor가 dopamine system modulation

, Kretschmer(2000) NMDA receptor antagonist ventral corticostriato - thalamocortical loop nucleus accumbens output structure ventral pallidum dopamine release가 가
 Deep (1999) PET
 amantadine striatum
 cerebral dopa decarboxylase (DDC)
 NMDA type glutamate receptor

Amantadine의 부작용(Adverse Effect)

Gualtieri (1989) insomnia, vivid dream, anorexia, hallucination, irritability, nervousness, agitation, disorientation, psychosis, hyperactivity, aggression, delirium, depression behavioral toxicity가 amantadine 가
 neuroleptics
 amantadine neuroleptic malignant syndrome neuroleptic - induced catatonia livido reticularis. blotchy skin rash, pendant edema
 가 . Amantadine
 seizure threshold seizure
 (Gualtieri 1989 ; Nickels 1994).
 amantadine intracranial pressure 가 seizure threshold 가
 .(Nickels 1994) Schwab (1972)
 amantadine
 Gualtieri (1989)
 amantadine
 Amantadine (Sartori 1984) phenelzine
 (Jack Daniel 1984). Nickels (1994) amantadine 12 mania, hypomania, pedal edema 3 generalized seizure 2 anticonvulsant
 seizure가 1 visual hallucination
 amantadine . Kr-aus Maki(1997) 7 aman-tadine
 가 am-

antadine
 amantadine
 agent amantadine
 (MMWR 1987 ; Atkinson 1986).
 amantadine
 가
 ins -
 omnia, jitter, poor concentration, depression
 vomiting, dyspepsia gastrointestinal effect
 가 (Kaplan Sadock
 1998). Psychosis
 가
 (Nickels 1994).

결론 및 요약

가
 . Amantadine presynaptic postsyn -
 aptic dopamine neurotransmission
 NMDA receptor antagonist ex -
 citotoxic substrate ne -
 uroprotective agent amantadine
 100mg 400mg
 (behavioral tox -
 가 4~7).
 icity가
 monitoring
 . amantadine sedating drug
 coma recovery
 가

중심 단어 : Amantadine . NMDA

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