# THE EFFICACY OF 7-METHOXYTACRINE IN THE TREATMENT OF CENTRAL ANTICHOLINERGIC SYNDROME CAUSED BY SOME INCAPACITATING CHEMICAL AGENTS

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***Summary***

*Central anticholinergic syndrome evoked by some incapacitating chemical agents from the family of anticholinergics is possible to treat with some reversible centrally active inhibitors of acetylcholinesterase. In this paper the view of anticholinergic incapacitating agents and their biological effects is summarize as well as a survey of inhibitors of acetylcholinesterase which may be used as antidotes against intoxication by incapacitating chemical agents. The position of 7-methoxytacrine as very effective and little toxic antidote is discussed.*

KEY WORDS: Incapacitating chemical agents; Biological effects; Acetylcholinesterase inhibitors; Antidotes.

## Introduction

Chemical weapons conceive uncommonly meaningful resource of army (1, 2). Besides classical chemical compounds with high lethality and mortality some agents were developed, which in relatively small doses caused psychical and physical harm to living power (2, 3). These compounds are known as incapacitating chemical agents (NCA) (2). From the military point of view the most important NCA are compounds with psychotomimetic effect (4, 5). These compounds are also known as psychodysleptics, fantastics, psychodelics, psycholytics or halucinogenes (6).

Well-known psychotomimetics are compounds pharmacologically characterized as anticholinergic drugs (7, 8).

## Anticholinergic NCA

There are compounds occurring in natural sources (belladona alkaloids atropine and scopolamine) from any *Solanaceae* (*Atropa belladonna, Hyosciamus niger* and *Datura stramonium*) (9, 10) and in chemically synthesized compounds as for example benactyzine, JB 336, Ditran or BZ (10-12). The chemical structures of all these compounds are given in Table I.

*Atropine*

is a racemic mixture of D- and L-hyoscyamine used as a drug in the form of the well-soluble hydrochloride. The minimal lethal dose for humans is 0.1 g (13), therapeutic doses are in the interval from 0.5 to 1 mg *pro dose* (6). Atropine is quite absorbed by mucous membranes. In small doses only peripheral effects were observed, in high doses central and incapacitating effects were also observed (14).

*Scopolamine*

structurally resembles atropine and as a drug is used in the form of soluble hydrochloride. Its toxicity is approximately five times higher than the toxicity of atropine (6). In higher, but not toxic doses, causes the same psychotic disorders as atropine and both drugs have been ever used for ritual and therapeutic purposes since antiquity (12, 15).

*Benactyzine*

was developed as a synthetic tranquilizer with anticholinergic action. Its psychotic effect resembles atropine and the central component of pharmacological effect outweigh the peripheral one. Benactyzine is also less toxic than atropine (16).

*JB-336*

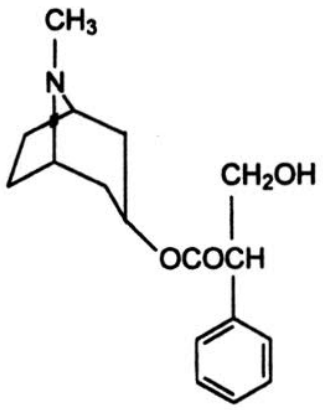
is one of many compounds prepared by John Biel (code JB) (17, 18). This compound is one of the most active derivatives of substituted piperidyl-benzilates (19, 20).

*Ditran*

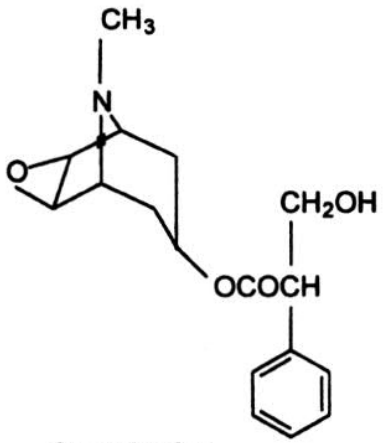
is a mixture of two compounds: 70 percent of N--ethyl-2-pyrrolidyl-methyl-cyklopentylphenyl glycolate and 30 % of N-ethyl-3-piperidyl-cyklopentylphenyl glycolate (21). It is used as soluble hydrochloride. Ditran was used as a model compound for the study of nervous system. It was used for experimental as well as for psychotherapeutic purposes (12, 22, 23, 24). Ditran was also extended among addicts for its hallucinogenic properties (6).

*BZ*

or QB are code names for 3-quinuclidinyl benzilate (25). This compound is relatively little toxic but psychical incapacitance appears already at its very low doses (26). There is a sole compound



**Atropine**



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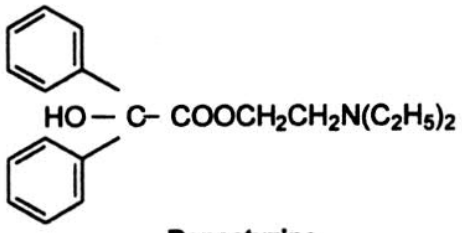
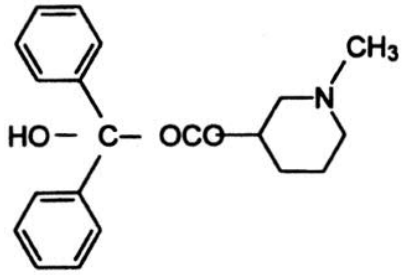
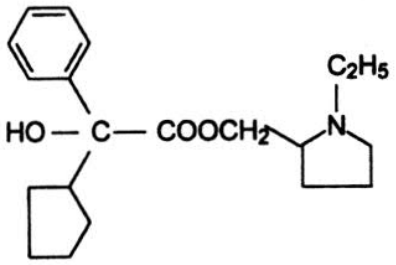


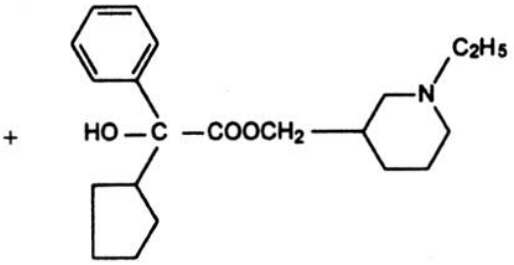
**Benactyzine**

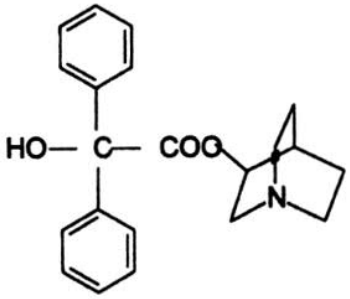


**JB-336**



**Ditran**





**3-Quinuclidinyl benzilate (QB, BZ)**

*Table I The chemical Structures of Some Anticholinergic Drugs which are known as Incapacitating Chemical Agents (NCA)*

NCA used in battle-field against people (27). The common mechanism of pharmacological effects of these compounds is founded in their interaction with acetylcholine receptors and subsequent depolarization of excitation membranes (11, 28). From the pharmacological point of view these compounds may be characterized as anticholinergics with psychotomimetic effect and different affinity to the central and peripheral nervous systems (9, 29-32).

## Clinical course of acute intoxication

Clinical course of intoxication with all these compounds is actually the same as with over-dosing of atropine or natural belladona alkaloids (33). Acute intoxication courses cover up changes in autonomous, motoric, central, neurological, behavioral, and psychological functions (26, 34, 35). The survey of these symptoms is summarized in Tables II and III.

Table II

**The Survey of Symptoms of Intoxication by Anticholinergic Drugs (NCA) - Autonomous and Neurological Symptoms**

| Changes in Functions | Symptoms |
|---|---|
| Autonomous peripheral | - mydriasis<br>- dryness in mouth<br>- hyperemia of skin<br>- tachycardia<br>- hypertension |
| Motorical and somatical | - retarded speech<br>- slow gait<br>- tremor<br>- rigidity |
| Senzoro-thalamical | - ataxia<br>- increase of sensitivity to pain<br>- loss of tactile and thermic receptivity |
| Telencephalical | - hypotonia<br>- fine tremor<br>- somnolence<br>- irritation<br>- excitation<br>- afasia<br>- apraxia<br>- visual and auditory agnosia<br>- disarthria<br>- loss of speech<br>- vertigo<br>- nystagmus |

The time course of acute intoxication is different for individual compounds. In the case of the most important NCA BZ, the first symptoms appeared 30 min after drug application. This first phase of intoxication has a vegetative character. Delirium phase of intoxication begins after 1 to 1.5 hrs and culmination of symptoms is observed between 4 to 8 hrs. The lethargical phase of intoxication develops usually after 12 to 24 hrs (12, 26). From this it is evident that the incapacitance of people caused by BZ is long-term (9). In the military context there are important effects of NCA based on the entire disorientation and the loss of contact with environment connected with harm of imagination and speech as well as the senses of desperation and anxiety (36). Therefore, it is very desirable to apply the effective antidote as soon as possible the best way is in the form of self-aid or fist-aid.

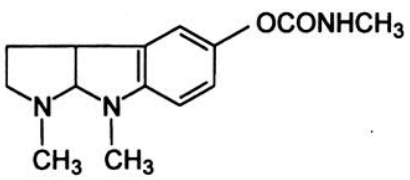
Table III

**The Survey of Symptoms of Intoxication by Anticholinergic Drugs (NCA) - Psychological and Behavioral Symptoms**

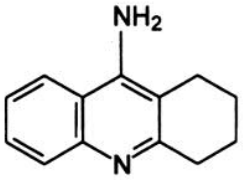
| Changes in Functions | Symptoms |
|---|---|
| Stupor | - damage of space and time cognizance<br>- retarded mental functions<br>- retarded reactions<br>- lack of interest<br>- incoherentia<br>- somnolence |
| Delirium | - absence of mind with agitation<br>- illusions<br>- apprehensions<br>- disturbances<br>- anxiety |
| Hallucination | - auditory<br>- visual<br>- tactile<br>- smell<br>- taste |
| Disturbances | - space and time disorientation<br>- erroneous interpretation of questions<br>- inability of orientation in life environment |
| Emotivity | - sudden spite or emotivity stroke<br>- negativism<br>- paranoic reaction<br>- sudden anxiety, scare, panic fear |
| Amnesia | - inability to remember |
| Dream states | - slight remembrances of the past<br>- delirium |
| Aphasia | - inability to coherent speech |
| Agnosia | - loss of ability to formulate thoughts<br>- complete inability to speak |
| Intellect | - decrease of rate and accuracy in solving problems<br>- inability to comprehend questions |

## Therapeutic drugs used as antidotes

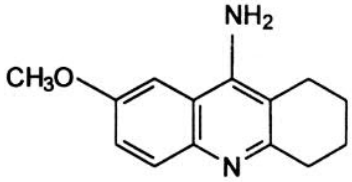
All therapeutic drugs used for the treatment of central anticholinergic syndrome are compounds with cholinomimetic effects. Only three compounds of this type were recommended as antidotes for the therapy of acute intoxication by NCA: Physostigmine, tacrine, and 7-methoxytacrine. All these compounds are both peripherally and centrally effective cholinesterase inhibitors which exert both peripheral and central cholinomimetic actions. The chemical structures of all these compounds are




**Physostigmine**




**Tacrine**




**7-Methoxytacrine**

*Table IV The Chemical Structures of Some Antidotes Used for Treatment of Anticholinergic Syndrome Evoked by Anticholinergic Drugs (NCA)*

given in Table IV.

*Physostigmine (eserine)*

is alkaloid from the plant *Physostigma venenosum* Balf. growing in West Africa and known here as Calabar bean (37). These beans were used in this geographical area of Africa for the poison ordeal (15). Physostigmine is widely used in modern medicine (38, 39) but its toxicity is too high. Therefore its numerous analogues used as cholinergic drugs were synthesized and evaluated (40-42). The acute toxicity of physostigmine in mice after i.m. application is expressed by $LD_{50}$ value of 0.6 mg/kg (41).

Antidotal effective dose of physostigmine in humans at NCA acute intoxication is 1 to 2 mg i.m. or i.v. and it is characterized by a short duration of action (≈ 50 min) (43). Therefore, repeated application is necessary for the effective therapeutic benefit (44). However, physostigmine is not an ideal drug for the treatment of acute intoxication caused by NCA because of its short duration of action, its strong peripheral side-effects and very narrow-therapeutical window (45).

*Tacrine (THA)*

9-amino-1,2,3,4-tetrahydroacridine was first synthesized by Albert and Gledhil (46) and it was originally developed as a partial antagonist of morphine (47). This compound can be obtained by several different methods (48-50). The acute toxicity of this compound is smaller than the toxicity of physostigmine ($LD_{50}$ i.v. in mice is 29 mg/kg) and also the duration of its pharmacological action is longer (51). Therefore only single dose of tacrine (30 mg i.v. or 60 mg i.m.) is sufficient for antagonizing of anticholinergic syndrome evoked by NCA. The side effects of tacrine are not very significant (45).

*7-Methoxytacrine (7-MEOTA)*

7-methoxy-9-amino-1,2,3,4-tetrahydroacridine is a simple derivative of tacrine. The compound was developed in our Institute (49), where many compounds of this type have been synthesized and tested as antidotes against NCA intoxication (52, 53). 7-methoxytacrine has been drawn for its low toxicity and good therapeutic effect. The $LD_{50}$ value in mice (i.v.) is 125 mg/kg (54). Also in other animal species the acute toxicity of 7-methoxytacrine was lower than the toxicity of tacrine (54). The time of course of the pharmaceutical action of 7--methoxytacrine has still a longer duration than tacrine (45). Therapeutic dose for humans is 50 mg i.m. or 100 mg p.o. This single dose is quite sufficient for antagonizing by NCA evoked anticholinergic syndrome. No side effects have been observed. There is a very important fact that 7-methoxytacrine is fully effective also in peroral application (55).

## The mechanism of antidotal action

All these compounds are based on their ability to inhibit the activity of cholinesterases, i.e. acetylcholinesterase (AChE, EC 3.1.1.7) and butyrylcholinesterase (BuChE, EC 3.1.1.8) (56-58). Physostigmine inhibits cholinesterases by acylation of mechanism, when active site of these enzymes is carbamoylated (59). The value of $pI_{50}$ for both AChE and BuChE is 7.00 (60). Tacrine and 7-methoxytacrine inhibit cholinesterases by other mechanism (57). These compounds bind to hydrophobic area localized on the surface of both enzymes and their mechanism of inhibition is allosteric (57, 61). The $pI_{50}$ values for tacrine were 5.62 for AChE and 6.96 for BuChE (57), $pI_{50}$ values for 7-methoxytacrine were

5.49 for AChE and 6.42 for BuChE (58). In all cases the inhibition effect is reversible. All three compounds also penetrate to brain across the blood-brain barrier and inhibit brain cholinesterases (59, 62). Accumulation of the acetylcholine on acetylcholine receptors, which is consequent to a cholinesterase inhibition, compete with NCA. There is the main mechanism of antidotal effect of these anticholinesterases (6).

It is interesting, that many anticholinesterases could be applicable to the therapy of diseases, characterized by the cholinergic deficit in brain. Best-known is the use of these compounds in the therapy of Alzheimer's disease and the dementia of Alzheimer's type (63-68). Therapeutic use of this drugs is based on the so-called cholinergic hypothesis of geriatric memory dysfunction which suggests that cognitive decline can be counteracted by enhancement of central cholinergic dysfunction (69, 70).

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