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Physostigmine salicylate as an antidote

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Abstract. Most poisonings with anticholinergics deal with simple cases without diagnostic or therapeutic difficulties; however, in difficult or unclarified cases a new method for diagnosis and treatment is the antidote physostigmine salicylate. Within 15 minutes after application of 2 mg of the antidote the central anticholinergic symptoms disappear, such as respiratory depression, coma, cramps and hallucinations as do the peripheral anticholinergic symptoms as cardiac rhythm disturbance, dry mouth and red dry skin. No fatal overdose with anticholinergic drugs occurs if the antidote is given in time.

Key-words: Physostigmine salicylate – antidote – anticholinergics.

The antidote physostigmine was isolated from an extract of Calabar bean (physostigma venosum) in 1855 by Christioson. Since 1863 physostigmine has been recommended in the international literature as an antidote for anticholinergic drugs in more than 200 papers [Argyll-Robertson 1863, Kleinwächter 1864]. In the German literature there were only a few papers about physostigmine as an antidote for tricyclic antidepressant drugs [Czech, Mühlendahl, Heimsoth, Schönhofer]. However, it is still maintained that there is no antidote for the dangerous cardiac side effects of tricyclic antidepressants [Rasenack 1974, 1976a, b, 1977]. Warnings against the use of physostigmine have been erroneous in cases of bradycardiac arrhythmias of the heart [List, Noble, Daunderer].

The danger of anticholinergic drugs

The use of psychotropic drugs is increasing in all industrial nations [Parry]. Severe poisonings with anticholinergic agents have a high mortality rate. Most fatal overdoses have been reported after the ingestion of about 2.5 g tricyclics. However, fatal doses have been reported to range from 1.5 to 2.5 g [Cutler]. A large dosage first causes a stimulation of the organism, then a depression leading to death [Innes]. Primary elimination of the poison can fail because of its central depressant effect and gastric lavage can come too late, since alarming symptoms first appear after absorption is finished. Furthermore, unforeseen grave cardiac symptoms often appear suddenly after a relatively long latent period [Heath, Hofnagel, Scally] and they are not influenced by the usual antiarrhythmic therapy or even by pacemakers [Ambani, Daunderer, Goel]. Cause of death is thought to be pulmonary embolism [Engelbrecht, Bismuth]. The greatest dangers are the unforeseen cardiac complications [Barnes, Bismuth, Brackenridge, Braun, Brown, Cainross, Crocker, Edwards, Fendrick, Freeman, Garrison, Glogner, Harthorne, Heiser, Horgan, Hucker, Kotzaurek, Krienke, Lamarche, Masters, Mocetti, Müller, Nymark, O'Brian, Rasmussen, Royds, Schober, Sedal, Serafimovski, Sigg, Sothall, Sunshine, Szeleso, Thomson, Williams, Würmli]. Young people have a greater chance of survival than older people or those with heart failure [Ayd, Degwitz, Gerlach, Sarby]. The mechanism of destructive action upon the heart by the tricyclic antidepressants has been described as necrosis of heart muscle [Sarby, Sigg, Thorstrand]. This is the explanation of death up to twelve days following poisoning [Brackenridge, Hell, Stell, Masters]. Early application of physostigmine prevents cardiac arrhythmia [Slovis]. From over 700 anticholinergic intoxications, which Rumack had treated with physostigmine, the most frequent effect was the removal of severe ventricular arrhythmia [Snyder]. Therapy with neuroleptic drugs causes convulsions and various extrapyramidal side effects such as early dyskinesia [Ernst, Meyer, Nobel]; these effects respond well to physostigmine. The coma following anticholinergic poisoning together with respiratory depression causes pneumonia, the probability of which increases with duration of intubation [Snyder]. Physostigmine immediately prevents the respiratory depression which was caused by anticholinergic drugs [Daunderer, Burks, Newton].

If administered just once, imipramine causes decreased serotonin assimilation and thus a rise in the serotonin level at the synapse [Burko] in contrast to

imipramine intake over a long period of time [Schildkraut]. Other effects include blocking of dopamine receptors as well as increase of noradrenalin at the receptor [Anden, Pscheid, Klawans, Laverty, Sulser].

A rise of acetylcholine in the limbic system [Schacht] simultaneously means an increased dopamine metabolism [Ambani, Anden, Hornykiewicz].

Physostigmine antagonizes biogenic amines such as dopamine, norepinephrine, histamine, and serotonin [Anden, Davis], especially in the corpus striatum and the limbic system. A cholinergic link initiates the release of catecholamines in the brain [Anden].

The opposing antagonism between central cholinergic and anticholinergic agents was also confirmed by EEG studies [Dasberg, Exley, Longo, Weiß, Williams]. With physostigmine the EEG shows a characteristic desynchronization and waves with lower frequence and voltage [Koelle]. Following desynchronization, cholinergic agonists and anticholinergics induce EEG seizures and motoric convulsions (petit and grand mal) when administered in large intravenous doses [Kotzaurek]. Physostigmine induces analgesia when used alone, or potentiates the action of narcotics and non-narcotic analgesics or both [Goldberg]; it has proved as potent as morphine. The use of physostigmine causes an increased fragility of erythrocytes [Greig] and thereby an outflow of sodium as well as an inhibition of T-lymphocytes by an inflow of membrane-bound cholinesterase on the receptors [Chandra]. In this context the relationship between manic psychosis and alteration of the sodium counter-current mechanism has been discussed [Parry].

While the effects and especially the side effects succeed in displacing central sympathetic or parasympathetic tone, physostigmine raises the parasympathetic tone and thus prevents these side effects [Modestin]. While the effect of physostigmine on the cholinergic and dopaminergic systems has been studied [Aquilonius, Gerlach], its effect on the noradrenergic and serotonergic systems is not yet known. However, we do know that all four systems influence each other [Schildkrauth, Tretter] and within that fact lies the key to its effects.

Table 1 Indication groups:

	References:
Amphetamines:	Bradley, Janowski
Antihistamines:	Ayd, Breivik
Antiparkinson drugs:	Argyll, Robertson, Ayd, Breivik, Crowell, Danowski, Forrest, Green, Holzgrafe, Innes, Koelle, Hrbek, Mühlendahl, Tarsy, Ullmann, Wilson, Young
Benzodiazepines:	Bernards, Blitt, Breivik, Katz, Liberty, Nagg, Rosenberg, Snyder, Schuster
Curare:	Katz, Feldberg, Herden
Ethanol:	Daunderer
Glutethimide:	Breivik
Neuroleptics:	Benesova, Breivik, Consroe, Rosenberg
Plants (atropine-like):	Breivik, Daunderer, Gowdy, Hall, Orr, Schmidt
Phenothiazines:	Ambani, Ayd, Bernards, Gershon, Heiser, Liberty, Jankowski, Rosenthal
Psychowar poisons:	Abood, Bell, Breivik, Gershon, White
Psychopharmacodelics:	Bernards, Crowell, Cutler, Janowsky, Klauber, Modestin, Mofenson
Tricyclic antidepressants:	Benesova, Bennett, Breivik, Burks, Czech, Dasberg, Daunderer, Duvoisin, Falletta, Holinger, Janowsky, Koelle, Manoguerra, Newton, Noble, Postlethwaite, Rumack, Slovis, Snyder, Schärer, Vaillant
No indication: Strychnine:	Baker, Ullmann, Goodman

Indications for physostigmine

Physostigmine is effective against intoxications of over 600 varieties of anticholinergic drug groups or plants [Daunderer] when inadequate elimination of the poison results from inforced diuresis, hemoperfusion, or hemodialysis [Asbach, Bernards, Borden, Harthorne, Hucker]. If the dose of anticholinergics was potentially lethal, the antidote physostigmine is the only therapy [Hartwich]. However, if after application of physostigmine the patient remains in a coma, inforced diuresis or dialysis is indicated as in cases of hypnotic drug intoxication.

Identification of a physostigmine indication

Prognostic conclusions cannot possibly be drawn from the level of tricyclic antidepressants in the blood serum, because an even distribution of poison follows as a result of the high tissue affinity to lipid-soluble substances [Ancker, Bickel, Burko, Glogner, Noble, Spiher]. In the organs, amitriptyline has 3–70 times its concentration in the blood level [Eschenhof].

Only a minimal amount of poison remains bound to serum proteins. The latter are excreted quickly, how-

ever, which explains the prolonged high urine level. While quantitative gas chromatography identification methods as a result of increased metabolites are rarely used, the substances can be identified through thin layer chromatography and in the urine by means of the Cronheim-Ware method, i.e., qualitative identification of basic compounds through formation of salts with the weak acid bromcresol purple and differentiation through typical absorption spectrum [Cronheim, Fendrick].

Due to difficult identification methods, the impossibility of another effective poison elimination, and the time factor involved in impending therapy-resistant cardiac rhythm disturbances, physostigmine assumes a special diagnostic significance. A therapeutic trial of physostigmine is safe; when effective, it is a diagnostic means for anticholinergic intoxication [Snyder]. Only for imipramine and phenothiazines in the Forrest reactions [Forrest] are there simple and reliable, quick identification techniques. In the same way alcohols can be easily identified with the Draeger gas detector.

Side effects

Subjectively, physostigmine causes body tension, discomfort, uneasiness, and depressive narrowing of the breast [Gerlach, Mofenson]. Objectively there is salivation, concentrated tracheobronchial secretions, miosis [Forrest], perspiration, shortness of breath, bronchial spasm, increased gastrointestinal secretion [Mahler], vomiting, stomach cramps, bradycardia [Granacher]; urine and feces continue to be frequently voided [Fraser]; with anticholinergic poisonings the blood pressure does not change after administration of physostigmine [Forrer]. Instead a normalization of a hyper- or hypotension occurs. While small physostigmine dosages stimulate breathing, toxic dosages lead to respiratory depression [Koelle]. Severe side effects after a single dose can trigger asthma seizures, respiratory standstill, cardiac arrest, or cramps [Granacher, Mofenson, Weiss]; the anticholinergic poison can also be responsible for the latter two. Atropine, the competitive antagonist to acetylcholine, at half the dosage of the previously given physostigmine (0.01–0.03 mg/kg i.v. or i.m.) immediately eliminates all muscarine-type side effects by increasing the acetylcholine concentration on the receptor site of the effector organs [Ayd, Granacher, Innes, Pasy, Weiss]. In almost 5,000 physostigmine applications no conflict was observed. If continuation of therapy is necessary where solely the peripheral side effects are to be treated, glycopyrrolat (Robinol) in a dose of $^1/_{10}$ to $^1/_5$ of the physostigmine dose can be used (e.g. 0.2 mg i.v. or i.m.) [Baldessarini, Granacher, Greenblatt, Gyermek, Shader, Klingemaier, Ramamurthy, Snyder]. For the patient in coma it may be wise to intubate him before giving physostigmine to avoid possible aspiration of vomit [Snyder]. In animal studies physostigmine was found to be teratogenic. From these studies it was determined that physostigmine should not be applied during pregnancy [Ayd]. Benzodiazepines, neuroleptics, or phenothiazines have no sedative effect when given in cases of poisonings with anticholinergically effective substances against states of agitation. On the contrary, these drugs increase excitation [Gershon, Greenblatt, Lee, Liberty, Mofenson, Mikolich] because they are effective in the same way as anticholinergic agents. For the same reason, alcohol intoxications should not be treated with anticholinergically effective substances. A severe physostigmine poisoning was successfully treated 75 min after oral intake of 1 g powdered physostigmine by applying gastric lavage with atropine and artificial respiration [Cumming]. Overdoses of up to 1,000 mg have been survived without sequelae [Snyder]. On the other hand, physostigmine significantly enhanced storage of information into long-term memory [Davis].

Physostigmine

Mechanism:

Anticholinergic drugs competitively block the effect of acetylcholine at synapses by binding to the post-synaptic receptor. Raising the concentration of acetylcholine in the synaptic cleft leads to reversal of this blockade. This increase in acetylcholine concentrations may be accomplished by the use of inhibitors of cholinesterase, the enzyme present at the post-synaptic membrane which hydrolyses acetylcholine into inactive choline and acetate [Snyder].

Physostigmine is a carbamate, i. e., a cholinesterase-inhibitor. After intravenous injection of 0.03 mg physostigmine/kg b.w., the cholinesterase in serum falls to $^1/_{10}$ of the former level within a minute (after i.m. application after 5 min) and at least 15 min later reaches the former level again [Engelbrecht, Rowentree]; 2–20 min later – usually after 8 min central (coma) and peripheral (cardiac arrhythmia) – anticholinergic effects disappear. The delayed effect of the antidote correlates with the delayed starting effect (hours to days) of the psychotropic agent. Physostigmine is a tertiary amine, soluble in lipids, which can pass through the brain-blood barrier in contradiction to the quaternary amines, pyridostigmine and neostigmine. Physostigmine therefore increases the level of acetylcholine in the brain [Forrer]. Physostigmine

changes EEG-lines [Bradley, Burney, Feldberg] to quick activities with small amplitudes and there is no wakening effect. Conversely neostigmine shows no alterations of EEG. When given physostigmine, patients with anticholinergic poisoning such as atropine or imipramine can move, sit up, answer questions about their intoxication and time of intake, even if unconsciousness and respiratory or cardiac failure had previously prevailed [Engelbrecht, Holzgrafe, Newton]. When the effect of anticholinergic drugs is less prominent, the effect of physostigmine is also not as great. Heart frequency during tachycardia may decrease by 20 beats per minute, blood pressure and respiratory volume will normalize.

Physostigmine is contained in leguminous semen such as calabar beans (esere nut, chop nut) and dioclea types [Fraser]. Its synthetic production: colorless crystals C 15 H 21 N 3, 02, MG 275, 34, indol-alcaloid. In Germany it is available as physostigminsalicylat at 2.5 mg in 5 ml or since Dec. 21, 1977 (Charge Nr. 355771) at 2.0 mg in 5 ml [Köhler 1978] through Dr. Franz Köhler Chemie, Alsbach.

Toxicity:

LD_{50} for mice amounts to 63 mg/kg. The animals die with cramps and arrest of respiration and circulation [Koehler].

Dosage:

For adults 2 mg, for children 0.02 + 0.06 mg/pro kg, i.m., i.v. in continuous intravenous application, percutaneously (Fraser) or orally [Aeschlimann, Forrer, Gowell, Koelle, Koehler]. The ampules must be protected from light and must not be heated. The half-life of physostigmine is 1½ hours [Goodmann]. With severe poisonings the antidote must be repeatedly given every one, two or four hours [Crowell, Engelbrecht, Heimsoth] because it is rapidly hydrolyzed by cholinesterase [Traber]. The antidote therapy may have to be continued for a few days. With premature discontinuation, myocloni, choreoathetosis, and possibly coma with respiratory and cardiac rhythm disturbances may reoccur [Forrer, Holinger].

Contraindications:

Physostigmine is contraindicated in cases of acute bronchial asthma, coronary disease, gangrene, mechanical obstipation and urinary restriction, and intoxication with esters of phosphoric acids and carbamates.

Physostigmine test:

With one central and two peripheral anticholinergic symptoms (Table 2) and without a history of present illness or poison identification, the diagnostic use of physostigmine is recommended. The physostigmine test is indicated after poison identification with one central and one peripheral anticholinergic symptom (Table 1).

After positive physostigmine test with decreasing effect of the antidote, therapy with physostigmine is to be continued.

Therapeutic dosage:

Repeated dosage of 10 ampules of physostigmine in 500 ml physiological NaCl solution in continuous drop infusion did not prove beneficial because the necessity of finishing the antidote therapy with physostigmine was often overlooked, and intoxications with physostigmine occurred.

Intravenous injection of the same dose that leads to a successful physostigmine test is recommended (adults 2 mg, children 0.02–0.06 mg/kg) to be repeated when one of the following symptoms reappears:

Table 2 Central and peripheral anticholinergic symptoms.

Central anticholinergic symptoms:
Respiratory depression
Coma
Stupor
Delirium
Shock
Disorientation
Impaired memory
Cramps
Babinsky test, positive
Choreoathetosis
Hallucinations (optic, acoustic)
Fear
Hyperactivity
Agitation
Uncoordinated movements (EPMS symptoms)
Peripheral anticholinergic symptoms:
Mydriasis
Sinustachycardia or other cardiac rhythm disturbances (bradycardia)
Ischuria
Absence of intestinal sounds
Hyperthermia
Dry mouth
Red dry skin
Flush

coma, hallucinations, breath depression, convulsions, heart rhythmic disorder.

If the new injection of physostigmine shows no effect, this signifies a negative physostigmine test, and the therapy with physostigmine should not be continued.

Therapy with physostigmine should take place under intense supervision (monitoring).

Dosage should only be large enough that the patient can be spoken to. He may still be a little somnolent.

Heart frequency should not drop below 60 beats/min.

Psychiatric indication:

Physostigmine eliminates the chorea in Huntington's chorea [Aquilonius, Duvoisin, Klawans, Tarsy], that caused by acute marihuana smoking [El Joussef, Freemann], and likewise a depression in manic-depressives and has furthermore been successfully used in the treatment of mania [Bowes, Caroll, Freemann, Janowsky, Rowntree]. With physostigmine, latent Parkinsonism can be exacerbated (Gerlach). The psychic symptoms occur some time before the somatic symptoms. Rosenthal found oral physostigmine [1973] (up to 15 mg/24 hr) helpful in five chronic schizophrenics refractory to phenothiazines. Physostigmine was used by Pfeiffer as a mood deviator and a drug facilitating wakefulness and learning.

Pyridostigmine, prostigmine:

Quaternary amines can eliminate peripheral anticholinergic symptoms such as mydriasis and cardiac rhythm disturbances; however, they have no effect on central anticholinergic symptoms.

Pyridostigmine is more effective than prostigmine. The two are contraindicated in the diagnostic treatment of coma or as therapeutics in respiratory depression or cramps.

Personal experience:

Physostigmine was used in 105 cases, of which 75 applications were successful; 30 applications were unsuccessful because the case history of the poisoning with anticholinergics was not appropriate. In 27 cases a hypnotic drug poisoning was confirmed or the preceding atropin injection (1 mg) before gastric lavage or intubation concealed the effect of physostigmine (see Table 3). Seven patients with pure alcohol intoxications, some with respiratory depression, were suddenly reactive after about 8 min, respiratory stable, and calm. Some cases showed a diagnostic degree of safety above six, and others of the Munich Poison Information Center, above five [Clarmann].

Table 3 Change of Reed Intoxication Stages after physostigmine.

I/0	II/0	II/I	III/0	III/I	III/II	Degree
6	9	5	12	14	2	Cases
IV/0	IV/I	IV/II	IV/III	V/0	V/I	Degree
3	10	4	3	2	5	Cases

Other therapies:

Despite the excellent therapeutic efficacy against massive oral poisonings with anticholinergically effective medications, a primary poison elimination through gastric lavage [Hartwich] when possible with the addition of polyethylenglycol and ending with charcoal – sodium sulfate salt instillation should always be done [Daunderer, Szeless]. Likewise of special importance are the acid-base balance [Brown, Prudhommeaux], electrolyte metabolism, (potassium) water balance, and replacing blood volume (plasma expander), as in usual intensive care therapy of severe poisonings. Cramps should not be treated with anticholinergics like benzodiazepines, but rather with barbiturates [Hall, Ullmanns]. With peripheral anticholinergic symptoms a quaternary carbamate-like neostigmine, pyridostigmine, or carbachole can, for diagnostic purposes, be used instead of physostigmine [Baldesarini, Granacher, Rasmussen].

Crossland found no change at all in the amounts of transmitter substances like acetylcholine or serotonin caused by the barbiturate abstinence syndrome but a quite striking change in the serotonin content of the brain in the ethanol abstinence syndrome; therefore serotonin metabolites may be responsible for some of the features of the ethanol abstinence syndrome.

Ethanol doses increase acetylcholine brain levels and physostigmine affects ethanol blockade of the release of acetylcholine from the brain. The blockade of a delirium tremens with physostigmine was described by Fraser [1863] for the first time. Physostigmine can be recommended for therapy of psychotropic agents and ethanol withdrawal delirium with hallucinations but not for withdrawal delirium of barbiturates, bromcarbamates, methaqualone, or diaethylen-pentenamide.

Table 4 Effect of physostigmine.

Poison	only one poison	first poison	further poison
Amanita pantherina	+		
Amitriptyline	+++	+++++++	++
Atropa belladonna	+		
Baralgin		+	
Biperiden		+	
Bromazepam			+
Carbromal withdrawal delir	+		
Chlorprotixen	+++		
Clomethiazol	+	+	
Clomethiazol withdrawal delir	+		
Clonazepam	+	+	+
Clozapin	+	++	+
Diamorphine withdrawal	+		
Diazepam	+	+++	++++
Diazepam withdrawal delir	+	+	
Dikaliumchloracepate	+	+	+
Dikaliumchloracepate withdrawal	+		
Diphenhydramine			++++++
Doxepine	+++	+++	+
Ethanol	+++++++	+++++	+++++++++
Ethanol withdrawal delir	++++++−		
Fenetylline		+	
Flupentixole			+
Fluphenazine			+
Imipramine	++		
Levopromazine		++++	+
Librax		+	
Limbatril	++	+++++	+
Lorazepam			+
Medazepam			+
Meprobamate	+		
Metoclopramide		+	
Nitrazepam			++
Nomifensin			+
Noramidopyrine			++
Oxazepam	+		+++
Perphenacin			+
Phenothiazine	+		
Prazepam			+
Prothipendyl	+	+	
Sulpiride			+
Thioridazine			++
Tranquo-Buscopan	+		
Trimipramine			+

Table 5 No effect of physostigmine.

Poison	only one poison	first poison	further poison
Barbiturate	– – –	–	
Barbiturate withdrawal	– –		
Bromcarbamides		– – – – –	
Bromcarbamide withdrawal	–		
Diethylpentamide		– – –	
Diethylpentamide withdrawal	–		
Diamorphine withdrawal sympt.	–		
Tilidine withdrawal	–		
Methaqualone	– – – –	– – – –	

Sign: + or –: is always one case.

Treatment for withdrawal: Crossland found that sleeping remedies like pentobarbital, chloralhydrate, or urethane, increase free, non-bound acethylcholine content in rat brains. Cholinesterase inhibitors have the same effect. Atropine, on the contrary, decreases the content of bound acetylcholine without influencing the free acetylcholine.

Procurement:

Although physostigmine is the oldest antidote (since 1864) and one of the most often used antidotes in clinical toxicology today, the conclusion to be drawn from the experiences of the Munich Poison Center is that this antidote is unknown to almost all physicians and its use overlooked in most life-threatening situations. In almost all cases where we recommended its application over the telephone, the callers asked us to apply the remedy and assume the responsibility. Even in the USA it is often regretted that this important antidote is so little known [Duvoisin, Weiss] and hard to obtain. Every physician should have physostigmine at hand. Physostigmine is being produced again since our introducing it on March 26, 1976 at the Congress of Anesthesia in Aschaffenburg/Germany [Daunderer] and can be obtained at any time at all pharmacies.

Summary

Most poisonings with anticholinergics deal with simple cases without diagnostic or therapeutic difficulties; however, in serious or unclarified cases elimination after reabsorption with forced diuresis or dialysis in severe cases is indicated. Otherwise the continued use of physostigmine is recommended.

Severe alcohol intoxications (over 4% in blood) show gradual improvement after repeated application of physostigmine.

After waking through a positive physostigmine test, the patient should remain in bed due to the danger of an orthostatic circulation collapse.

With repeated use of physostigmine, an overdose causing bradycardia should be avoided by inspecting further indications before the injections.

The antidote therapy of a clomethiazoline intoxication brought no uniform results and therefore cannot be recommended as a routine method.

Alcohol withdrawal delirium with hallucinations responds well to physostigmine, especially if it is applied soon enough. When myokinetic uneasiness prevails, barbiturates or chloralhydrates must be given in addition. The question of different delirium types must also be examined. In our experience there are alcohol withdrawal deliriums which respond well to atropine, and others which respond well to a combination of atropine and physostigmine.

Withdrawal deliriums which have a latent period of 5–10 days can be distinguished by a physostigmine test with benzodiazepine (withdrawal delirium positive) from a deep sleep due to tablet withdrawal delirium (negative) because the poison level in blood during delirium is constantly negative.

No awakening from coma, respiratory depression, or cramps is to be expected after infusion with prostigmine.

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