Review Paper

Toxic Nephropathies of Anticholinesterase Compounds

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ABSTRACT

Nephrotoxicity is not generally recognized as a major clinical feature of anticholinesterase (AntiChE) compound poisoning. While very few case reports and experimental data are available on the topic, clinical reports suggest that the nephrotoxic effects of antiChE agents may be more common than is commonly believed. The effect of antiChE agents on the human kidney has not been carefully or thoroughly evaluated. Limited experimental data indicate that acetylcholine (ACh) which accumulates in the presence of antiChE agents, as well as antiChE agents themselves, can significantly alter renal function. This may result from alterations in neural, humoral, and metabolic activity. Some experimental data also indicate that antiChE agents may have direct nephrotoxic effects on renal tubules.

This article aims to highlight antiChE agents as potential nephrotoxins. Further work is needed to explore the potential nephrotoxicity of antiChE agents in humans. Patients need to be more closely and carefully evaluated for evidence of nephrotoxic injury.

Key Words: Anticholinesterase compound, Organophosphate, Nephrotoxicity, Toxic nephropathy

Introduction

The kidneys being primarily excretory organs, are often exposed to exogenous toxins that enter the blood stream. Various kinds of substance exposure, as well as therapeutic medications represent potential sources of nephrotoxicity.

Nephrotoxicity can be defined as a renal disease or dysfunction that arises as a direct or indirect result of exposure to drugs, or industrial or environmental chemicals/ pollutants. It is well established that toxic nephropathies are not restricted to a single type of renal injury. Some chemicals target one discrete anatomical region of the kidneys, and may affect only one cell type. Chemical insult to the kidneys may result in a spectrum of nephropathies that are indistinguishable from those that do not have a chemical etiology.[1]

Nephrotoxicity is not generally recognized as a major clinical feature of anticholinesterase poisoning. Very few case reports and experimental data are available on the topic. However, clinical experience of late suggests that antiChE agents may have significant nephrotoxic effects. The effect of antiChE agents on the human kidneys has not been carefully or thoroughly evaluated so far. There is a lack of sufficient information in the literature characterizing the potential nephrotoxic effects of these agents.

Studies have indicated that both renal circulation and electrolyte excretion may be partially under cholinergic control, which suggests that antiChE agents could possibly disrupt normal renal function. Coupled with biochemical and histopathological changes consistent with neph-

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rotoxicity after the administration of antiChE agents, this supports the contention that a nephrotoxic action may exist in humans. In view of the widespread distribution of cholinergic neurons, antiChE agents as a group have received extensive application as toxic agents, in the form of agricultural insecticides and chemical warfare "nerve gases."[2] Specific antiChE action is shared by the following substances: organophosphates, carbamates and carbamoyl fluorides, quaternary ammonium bases, phenothiazines, nonphenothiazine antihistaminics, sulphonylfluorides, methanesulphonic acid esters, alkylsubstituted 2-aminoethanols, polychlorinated ethanes and tetanus toxin.[3]

Discussion

Kidney Function and Nephrotoxicity

The kidneys have important metabolic and regulatory functions to maintain body homeostasis that make them particularly susceptible to the toxic effects of chemicals. Many substances cause or aggravate renal dysfunction. The kidneys are particularly vulnerable to toxic injury for four reasons: (a) they receive 20–25% of cardiac output, yet make up less than 1% of total body mass; (b) they are metabolically active, and thus vulnerable to agents that disrupt metabolism; (c) they remove water from the filtrate and may build up a high concentration of toxic substances, and (d) the glomeruli and interstitium are susceptible to attack by the immune system.[4] The human kidneys are exposed to toxicants to a greater degree than other organs as they receive a disproportionately large blood supply. Renal concentrating mechanisms can lead to higher concentrations of substance in the tubules or interstitium, than in the blood. Specific transport mechanisms for secretion and re-absorption can result in a toxicant accumulating in tubular cells. The lipophilicity of antiChE agents may allow their penetration through plasma membranes with direct access to the intracellular space and organelles. It is reported that after acute human organophosphate (OP) poisoning, greater levels of OP are found to be localized in the kidneys than in blood.[5]

The kidneys are capable of oxidation, reduction, conjugation, and enzymatic metabolism. Although many of these reactions detoxify substrates, some metabolites or conjugates may be more toxic than the parent compound. Covalent binding of reactive metabolites to tissue macromolecules accounts for the toxicity of many chemicals. It has been suggested that O,O,S-trimethyl phosphorothioate (OOS-Me), an impurity in some antiChE agents, is metabolically activated to reactive metabolites that bind to tissue macromolecules, including those in the kidneys.[6] It is probable that, for instance, binding of malathion to tissue macromolecules is dependent on mixed function oxidase activity.[7]

Toxicants may cause direct tubular or glomerular injury, causing impaired secretory and reabsorptive function, or glomerular permeability. Prolonged vasoconstriction, either as a direct effect or compensatory mechanism, may lead to renal ischaemic damage. The high metabolic capacity and oxygen consumption of the kidneys make them more susceptible to hypotension, or altered neural or humoral activity. Nephrotoxic insults can occur, therefore, secondary to complications of antiChE poisoning such as hypotension or dehydration. Other complications such as muscle fasciculations and seizures can lead to rhabdomyolysis associated with myoglobinuria and acute renal failure. Such effects could also potentiate or unmask an otherwise clinically insignificant nephrotoxic potential of the antiChE agents themselves.

The renal cortex is extremely susceptible to toxic injury because it receives the greatest blood supply. The proximal tubule is most commonly affected. Resultant toxicity ranges from minor changes in cellular morphology and transport capabilities, to tubular necrosis.

Parasympathetic Control of Renal Function

It is known that the kidneys contain adrenergic nerve fibres, but the presence of cholinergic nerve fibres remains in question.[8] Acetylcholinesterase (AChE)-containing nerve fibres have been demonstrated in the kidneys of various mammalian species.[9-11] Nerves that contain a high concentration of AChE would be expected to be cholinergic nerves. An assessment of the nephrotoxicity of antiChE agents, therefore, must take into account the effects of ACh on renal function. The corresponding distribution of AChE-containing fibres with adrenergic nerve fibres has led to the suggestion that ACh may play a role in adrenergic neurotransmission by releasing noradrenaline. The presence of AChE-containing fibres after adrenergic denervation suggests that the kidneys contain two types of nerve fibres.

The effect of ACh on adrenegic transmission to the renal vasculature has been specifically evaluated. Takeuchi et al[12] studied renal vascular response to stimulation of the greater splanchnic nerve under various conditions in an attempt to demonstrate a cholinergic component. Neither the antiChE neostigmine, nor hemicholinium bro-

mide, drugs interfering with the production of ACh, had a consistent effect on the renal vasoconstrictor response to nerve stimulation. In addition, a vasodilator response was not elicited when the vasoconstrictor response to nerve stimulation was abolished with reserpine and guanethidine. ACh infused directly into the renal artery, however, did produce vasoconstriction that was reversed by atropine. It was concluded that antiChE fibres in the kidney are separate from adrenergic fibres.

In contrast, McGiff et al[13] demonstrated that ACh injected into the renal artery at high doses (1000 μg) produced vasoconstriction, whereas vasodilation resulted at low doses (1–10μg). The vasoconstrictor response was enhanced by co-administration of atropine and physostigmine at all doses studied, except 1μg. Reserpine, which depletes stores of catecholamines, caused ACh to produce only vasodilation. The use of autonomic blocking drugs either reversed or reduced the vasoconstrictor response to ACh. Physostigmine enhanced the vasoconstrictor response to nerve stimulation, whereas atropine diminished the vasoconstrictor response. Hemicholium bromide blocked the renal vasoconstrictor response to repetitive nerve stimulation, at which point ACh was probably depleted. It was concluded that the vasoconstrictor effect of ACh was probably caused by release of catecholamines. When paraoxon was infused to the point of systemic toxicity, it produced marked bilateral renal effects, including vasoconstriction. This resulted in decreased effective renal plasma flow (RPF) and glomerular filtration rate (GFR).[14]

Based on these studies, it can be inferred that the kidneys may be innervated by both adrenergic and cholinergic nerve fibres. The adrenergic pathway may be controlled in part by cholinergic stimulation, which may be dose dependent. It is difficult, therefore, reliably to predict the effect that antiChE agents might have on the renal vasculature. The apparent existence of cholinergic mediated adrenergic transmission within the kidneys, however, suggests a potential for deleterious effects of renal function in the presence of excess ACh. Increased renal adrenergic tone could contribute to acute tubular necrosis secondary to increased renal vascular resistance, activation of the renin-angiotensin system, or possibly increased transmembrane transport of calcium (Ca^{2+}) in renal tubular cilia.[8] Both increased vascular resistance and activation of the renin-angiotensin system may lead to renal failure secondary to a direct ischaemic insult. Increased intracellular Ca^{2+} is associated with lethal cell injury, but the precise mechanism has not been established.[15]

AntiChE Effects on Renal Excretory Function

The effects of ACh and antiChE agents on renal excretory function demonstrate further evidence for cholinergic control of renal function. These findings suggest a cholinergic control of cellular cation transport systems.[16] Urinalysis findings provide evidence for antiChE-induced nephrotoxicity. The kidneys contain OP-sensitive esterases.[17] Electron microscopic radiographs have identified radiolabelled diisopropyl fluorophosphates (DFP) localised primarily over the cytoplasm of proximal tubule cells, particularly with infolds of the basal plasma membrane, and small amounts either in, or on the mitochondria and microvilli. There was also heavy labelling of renal tubule cell nuclei. ChE activity has been associated with sodium (Na^+) transport in various tissues.[18,19] ChE activity has also been shown to be prominent in the thick ascending limbs of the loop of Henle in the rat kidney.[20] This suggests that ChE may be involved in Na^+ transport, associated with the counter current mechanism for concentrating urine in the renal medulla.

Data indicate that ACh directly affects renal excretory function. When ACh is infused into the renal artery, it produces a significant increase in water excretion, potassium (K^+), Na^+, chloride (Cl^-), Ca^{2+} and phosphate.[16,20-21] It also increases RPF, but produces variable changes in GFR. Urine osmolarity is decreased by ACh. These effects on renal function are blocked by atropine. It appears that ACh increases both efferent and afferent arteriolar vasodilation, as GFR remained stable or was variably affected. The fact that Na^+ excretion is increased despite unaltered GFR indicates that ACh inhibits tubular Na^+ reabsorption. Increased Ca^+ and phosphate excretion suggests a proximal tubular effect.[16] It has also been postulated that these effects are secondary to increased renal medullary blood flow, which would reduce the medullary osmotic gradient.[20]

Physostigmine, DFP, neostigmine methylsulphate, and paraoxon do not produce similar effects on renal function, even when administered to the point of systemic toxicity.[14,16,21] Atropine, administered alone, also failed to demonstrate any effects. These results suggest that either there is a lack of endogenous ACh in the renal system, or the renal ChE is resistant to these inhibitors, or that antiChE agents could not reach renal cell ChE. It has been suggested that this lack of effect may be from

antiChE effects on two opposing systems: enhanced ACh at postganglionic receptors and enhanced release of noradrenaline at adrenergic sites.[14] Sympathetic stimulation produces Na^+ and water retention, whereas parasympathetic stimulation causes increased water and Na^+ excretion.

Another approach to assess the effects of chemicals on renal function is the use of isolated renal tissue. The active secretion of the organic anion, para-aminohippurate (PAH), and organic cation, tetraethylammonium (TEA) is reduced by nephrotoxins. These two distinct processes may be evaluated in vitro by using the renal slice technique. Reduced uptake of these substances in vitro corresponds to impaired proximal tubular secretion in vivo. Baggett et al[22] studied renal cortex slices from rats, and the addition of DFP to fresh cortex slices, and found that PAH accumulation was decreased. Only the in vivo study demonstrated inhibition of TEA transport. These results suggest that DFP may have a selective action on renal organic ion transport. This selectivity may also relate to intrarenal distribution of DFP rather than a selective action of DFP on a specific transport system. Na^+ and K^+ content, inulin space, and total renal water were not altered. This indicates that normal tissue function was maintained.[23]

Further evidence that the effects of OPs on Na^+ excretion is from direct effects on tubular membranes is provided by low dose parathion studies in the dog.[24] Intravenous parathion (1.5µg/kg) significantly increased urinary Na^+ excretion, which was completely blocked by atropine; K^+ excretion was significantly decreased. Values for RPF, GFR and urine output either did not vary significantly, or was slightly decreased. AChE activity in both RBCs and renal tissue was not changed. Therefore, the effect on Na^+ excretion is probably a result of decreased tubular reabsorption secondary to changes in the tubular membranes, and is unrelated to enzyme activity. Gauna et al[24] proposed that the effect of atropine was due to its ability to block endogenous ACh.

In unanaesthetized animals, the effect of DFP (2,3 or 4mg/kg) on renal function was evaluated.[25] Urinary excretion of Na+, glucose, blood and protein was increased. Urine flow increased significantly, and was accompanied by a significant decrease in osmolarity. In anaesthetized animals, neither blood flow, nor GFR showed consistent changes. Increased urine output, regardless of changes in GFR or blood flow also suggests a direct tubular effect of DFP.[25] The renal ChE remained decreased when renal function parameters had normalized. This substantiates the belief that the effects of DFP are unrelated to its antiChE activity, but are the result of a direct effect of this reactive compound. The concomitant increase in the excretion of glucose, protein, and blood suggests the occurrence of acute renal damage. Increased excretion of protein, glucose, blood, and concomitant oliguria also occurred in rats administered parathion.[26] This was associated with renal histopathological changes.

O,O,S-trimethyl phosphorothioate (OOS-Me) is an impurity of malathion that potentiates the toxicity of malathion, and induces toxicity to rats when administered alone. A dose-dependent hyperaminoaciduria has been demonstrated in rats treated with 10-60 mg/kg of OOS-Me.[27] At higher doses (40-60 mg/kg), urine volume was decreased. The blood urea nitrogen to plasma creatinine ratio was used to distinguish between pre-renal, renal or post-renal OOS-Me damage. In most cases, this ratio was <15:1 indicating renal tubular damage. Such damage may account for the increased excretion of amino acids. To evaluate further the nephrotoxic effects of OOS-Me, an analysis of urinary proteins was performed.[28] Urinary amino acids, glucose, and specific gravity also were measured. There was substantial increase in urinary amino acids, and no change in total protein (but the types of protein were changed, most notably, a reduction of $gamma_1$-globulin). Urinary glucose was increased, and the specific gravity was only 1.01 in the presence of oliguria. These findings provide additional evidence that OOS-Me causes proximal tubule damage. It was suggested that OOS-Me might have effects on both the cellular and humoral immune systems.

Histopathologic Evaluations of Nephrotoxicity

Histopathological studies have been performed to examine changes of the kidneys when exposed in vivo or in vitro to antiChE agents. Although this does not provide much insight into possible mechanisms of antiChE nephrotoxicity, it gives valuable information about sites and types of injury. Several studies to assess the mammalian toxicity of carbaryl demonstrate diffuse cloudy swelling of proximal tubule cells.[29] The distribution of such swelling was more diffuse in animals receiving higher doses. Cloudy swelling of renal tubules was also demonstrated in rats dying after oral parathion.[26] The kidneys also had capillary-venous congestion, and there was fatty degeneration or necrosis of the tubules. There was no signifi-

cant change in kidneys of surviving animals. Chlorpyrifos also causes cloudy swelling of convoluted tubules.[30] An experimental study in rats showed that organophosphate can cause acute renal tubular injury.[25]

Further evidence of nephrotoxic action of carbaryl was the deposition of fine fat droplets in the epithelial cells of proximal tubules.[29] A similar deposition of fat occurred with triorthocresyl phosphate. Fatty degeneration of kidneys has been reported with soman and paraoxon.[31,32]

Degenerative changes of renal tubular epithelium from chronic administration of phosdrin to dogs and rats have been described.[33] Oxydemeton-methyl has also been shown in poultry to cause coagulative necrosis in tubular epithelial cells, and hyperplasia of endothelial cells leading to increased cellularity in the glomeruli.[34] Fenthion did not cause such degenerative changes. Both acute and chronic administration of oxydemeton-methyl and fenthion slightly increased the total lipid content of the kidneys, but decreased phospholipids. The ratio of phospholipids to cholesterol in the kidney was decreased by oxydemeton-methyl. This effect predisposes cell membranes to degeneration, which may explain the relative degenerative effects of the two OPs.[34]

Acute administration of phosmet produced renal vascular dystrophy, and degeneration of proximal tubule cells within 60 min.[35] The kidneys revealed signs of parenchymal and vacuolar dystrophy. Lysosomes accumulated in enlarged intracrystal spaces of mitochondria. Endothelial destruction of small arteries and of the basal lamina in capillary loops was also described. Evaluation after 24h revealed parenchymal dystrophy in the cells of proximal tubules. The cytoplasm of tubular cells contained numerous lysosomes and large vacuoles. Dense granules were evident in podocyte pedecelles, and cells of the juxtaglomerular apparatus.

Granular dystrophy in human and rat kidneys after intoxication with trichorfon and malathion has been reported.[36] Vacuolisation of podocytes, and destruction of tubular epithelial mitochondria occurs accompanied by increased lysosomal activity after administration of pinochelin ether of methylfluoride-phosphoric acid (PEMA).[37] Vacuolization of proximal tubule cells of monkey and rat kidneys has been described with the administration of carbaryl.[38] The parenchymal dystrophy and vacuolization may explain the increased excretion of blood, glucose, and protein in urine.[35]

The glomeruli have also been affected in antiChE nephrotoxicity. Although the renal parenchyma of rats was normal with the administration of phosphamidon, occasional foci of glomerulonephritis were reported.[39] Twice weekly administration of parathion caused proliferation and fibrosis of reticulin fibres of the basal membrane of Bowman's capsule and tubules.[40] This was most evident in rats receiving 8mg/kg and surviving for 200 days.

Another method used to assess nephrotoxicity has been measurement of renal enzyme activity. Impaired alkaline phosphatase activity indicates that transphosphorylation reactions may be adversely affected.[41] Increased acid phosphatase activity may be associated with cell disintegration and prenecrotic changes in renal tissue. The administration of malathion, phosalone, or phenthoate to rats significantly inhibited alkaline phosphatase activity. A significant increase in acid phosphatase was produced by malathion and phosalone, and a highly significant increase resulted from phenthoate administration. The administration of malathion with differing dietary levels of protein produced variable changes in alkaline phosphatase activity.[42] Alkaline phosphatase was increased in the 5% and 20% dietary protein groups, but decreased in the group receiving 10% protein. In a study using single doses of carbaryl, or daily doses for 7 days, acid phosphatase activity was significantly increased in rat kidneys, but alkaline phosphatase activity was unaffected.[43] The administration of malathion has also been reported to cause increased acid phosphatase activity.[44] These alterations in renal enzyme activity suggest a potential nephrotoxic action of antiChE agents.

Experimental evidence shows little correlation between renal tubular necrosis and the degree of OP-induced AChE inhibition, the main mechanism of OP toxicity, suggesting the involvement of alternate mechanisms. Since reactive oxygen species (ROS) are known mediators of many toxin-induced renal injuries, this study was conducted to investigate whether ROS played a role in bidrin (BD)-induced renal tubular epithelial cell (LLC-PK1) toxicity. BD is an OP insecticide formulation with dicrotophos as the active ingredient. These results demonstrate that BD can cause direct tubular cytotoxicity, and indicate, at least in part, a role for ROS and accompanying lipid per oxidation in cytotoxicity. Based on these direct in vitro findings, it is hypothesized that, besides hypotension that often accompanies OP intoxication, OP-induced oxidative stress at the tubular level may play a role in the pathogenesis of acute tubular necrosis.[45]

Evidence of Nephrotoxicity in Humans

Reports of human cases of accidental or intentional exposure to antiChE agents often only mention dramatic and clinically significant toxicity, and subtle effects may be disregarded or overlooked. One controlled study on humans suggests that impairment of renal function may occur without other objective or subjective findings.[46] Two groups of five men ingested either a placebo capsule, or capsules containing 0.06mg/kg carbaryl on a daily basis. Two other groups of six men ingested either a placebo, or 0.13mg/kg of carbaryl daily. Neither plasma, nor red blood cell ChE activities were significantly affected. No signs or symptoms attributable to antiChE effects were detected. Haematology, blood chemistry, and urinalysis revealed no significant effects. The only variable affected by carbaryl was the ratio of urinary concentration of amino acid nitrogen to that of creatinine in the group receiving the higher dose. This evidence indicates a slight impairment of the reabsorptive capacity of the proximal tubule.

Renal function evaluated in 30 children who received trichlorfon for the treatment of schistosomiasis did not show any nephrotoxic effects.[47]

Only a few reports of renal involvement with antiChE poisoning have been reported in medical literature. The first involved a 65-year-old man who developed acute renal insufficiency and massive proteinuria 4 weeks after he began heavy use of malathion, with intermittent dermal and inhalation exposure.[48] He presented with gross peripheral oedema. Pertinent initial laboratory data included the following: serum creatinine - 380mol/l (5.0µmg/dl), and serum urea nitrogen - 18.0 mmol/l (50 mg/dl). Urinalysis revealed 4+ proteins, four to five white blood cells, and three to four RBCs per high power field, and occasional granular casts. Renal biopsy evaluation by immunofluorescence revealed sparse deposits of IgG in glomeruli. Electron microscopic evaluations demonstrated uncovered, segmental, epimembranous electron-dense deposits, and diffuse effacement of the foot processes. His renal function gradually improved spontaneously. The authors suggest that the presence of membranous glomerulopathy, and low C_3 level 110 (normal range 115-328), indicates that malathion caused an immune complex nephropathy. They propose that an OP could invoke an immune response, with the insecticide serving as an antigen, or that the toxicity of the insecticide could unmask antigens. This is consistent with the findings of Keadtisuke and Fukuto[28] who suggest possible involvement of the immune system with the nephrotoxic effects of OOS-Me.

Another report describes a 26-year-old man who ingested approximately 8 ounces of a solution (of unknown concentration) of diazinon in a suicide attempt.[49] He developed significant muscarinic effects that were relieved by atropine and pralidoxime (2-PAM). His urine output shortly after admission averaged only 22 ml/h, and was dark and cloudy. Urinalysis on the second hospital day revealed trace protein, trace blood, moderate amorphous crystals, and a specific gravity of 1.029. Urine output increased with IV fluids. The crystalluria gradually resolved by the ninth hospital day. The composition of the crystals was not identified. AntiChE agents can increase Ca^{2+} excretion, which may have formed the crystals. It is unlikely that diazinon reached high enough concentrations in the urine to form crystals.[48] Diazinon, or its metabolites may have been partially responsible for the dark colour of the urine. It is possible that significant dehydration could have precipitated this reaction.

In a multi-hospital study of OP poisoning, renal impairment was reported in seven of 53 patients studied.[50] Renal dysfunction was associated with urinary sediment and decreased GFR. Seizures and coma occurred in 32 patients. Cardiac arrhythmias occurred in 22 patients. The incidence of hypotension was not reported. A pre-renal aetiology is likely to be responsible for the renal impairment in many of these cases.

Glycosuria (renal), albeit transient, was noted in a proportion of subjects admitted with organophosphate and carbamate poisoning. The exact aetiology of this is unclear, but in the light of recent literature, it is likely that oxidative stress at the renal tubular level leading to renal tubular damage may be the most likely explanation. Further, larger studies are needed to elucidate this in detail.[51]

A study has been conducted by the first author to evaluate the deleterious effects of organophosphate pesticides in occupationally exposed individuals.[52] The various parameters of renal function such as serum urea, creatinine, and uric acid were analyzed. The mean levels of all the parameters were within normal range, except serum urea which was slightly lower, and uric acid which was significantly higher in occupationally-exposed individuals, as compared to those who were non-exposed.

Conclusion

The aim of this article is to highlight antiChE agents as potential nephrotoxins. Clinically significant nephrotoxicity is an uncommon manifestation of antiChE toxicity, but it is possible that subtle nephrotoxic injury goes undetected in many cases. Clinical manifestations of antiChE poisoning such as hypotension, dehydration, and seizures can lead to nephrotoxicity, and could precipitate or unmask direct toxic effects.

Available experimental data indicate that ACh which accumulates in the presence of antiChE agents, and antiChE agents themselves, can significantly alter renal function. This may result from alterations in neural, humoral, and metabolic activity. Some experimental data also indicate that antiChE agents may have direct nephrotoxic effects on renal tubules.

It is imperative that further work is undertaken to explore the potential nephrotoxicity of antiChE agents in humans. Patients need to be more closely and carefully evaluated for evidence of nephrotoxic injury by clinicians treating such cases.

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