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Thiamethoxam, a Neonicotinoid Poisoning Causing Acute Kidney Injury via a Novel Mechanism

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INTRODUCTION

Human self-poisoning with insecticides is common in every part of the world because of their easy availability, and more so among farming households. Commonly used insecticides for this purpose are organophosphates and carbamates. Due to the high human toxicity of these agents, newer agents called neonicotinoids have been invented, which are relatively more toxic to insects and less toxic to humans and other mammals, partly because of their lesser interaction with vertebrate's nicotinic receptors and the inability to penetrate the mammalian blood−brain barrier. However, their breakdown products can cross the blood−brain barrier, resulting in human effects. There are 3 generations of neonicotinoids, with thiamethoxam belonging to the second generation. Most human toxicity data are available only for poisoning by imidacloprid, which belongs to the first generation.[1] In India, 7 cases of neonicotinoid overdoses have been reported so far. However, renal dysfunction is rare, with only 4 reported cases, all due to indirect causes; 2 cases are attributed to rhabdomyolysis,[2,3] 1 case to leucocytoclastic vasculitis,[4] and 1 to secondary sepsis.[5] Here we report a case of thiamethoxam poisoning causing acute kidney injury by direct toxicity, resulting in acute tubular necrosis.

CASE PRESENTATION

The patient's informed consent was obtained for the publication of his medical details. The patient was a 60-year-old farmer with an alleged history of consumption of 5 g of thiamethoxam 25% water dispersible granules (Figure 1) mixed in 200 ml of water as a means of deliberate self-harm. He was asymptomatic for initial 2 days, after which he developed nausea, vomiting, and abdominal pain. Subsequently, he had oliguria for 1 day and was anuric for the next full day. On admission, he was afebrile with a pulse rate of 60 beats/min, blood pressure 150/80 mm Hg, respiratory rate 20 breaths/min, SpO_2 99% in room air, and capillary blood glucose 102 mg/dl. Systemic examination results were normal, including normal neurological examination. Arterial blood gas analysis showed compensated metabolic acidosis. Initial blood investigations revealed Hb of 12.9 g/dl, erythrocyte sedimentation rate 60 mm/h, white blood cells 11.1 × 10^9 cells/mm^3, urea 11.32 mmol/l, creatinine 698.37 μmol/l, uric acid 463.98 μmol/l, sodium 129 mmol/l, potassium 3.5 mmol/l, chloride 93 mmol/l, bicarbonate 18 mmol/l, calcium 2.071 mmol/l, magnesium 0.97 mmol/l, phosphorus 1.03 mmol/l, total protein 5.7 g/dl, albumin 2.8 g/dl, globulin 2.9 g/dl, creatine phosphokinase, 77 IU/l , lactate dehydrogenase, 222 IU/l, serum amylase 33 IU/l, and serum lipase 19 IU/L. Urine examination revealed 2+ proteinuria with plenty of red blood cells on microscopic examination. The patient was initiated on fluid challenge, and as there was no improvement in urine output, hemodialysis was initiated. After 2 sessions of hemodialysis, his urine output improved. Renal biopsy was performed to determine the cause of acute kidney injury and revealed light microscopic changes of a few swollen tubular epithelial cells with cytoplasmic vacuoles, mild lymphocytic infiltration in the interstitium (Figure 2), and interstitial fibrosis with tubular atrophy in less than 5% of the core.

Figure 1. Granules of thiamethoxam 25% water dispersible granules.

Immunofluorescence was negative for IgG, IgM, IgA, C3, C1q, kappa and lambda light chain, suggestive of acute tubular injury. After a few days, the patient became dialysis independent, with improvement in renal function. A week later, during review, his renal function had recovered to a serum creatinine value of 97.24 μmol/l, and urine proteinuria resolved completely. His renal function was stable during subsequent follow-up after 3 months.

DISCUSSION

Acute kidney injury due to insecticide poisoning is very rare, even with organophosphates or carbamate poisoning. Neonicotinoids are usually less reported to have mammalian toxicity effects, although the recent increase in their use has caused various side effects.[1] Renal dysfunction due to secondary causes are reported predominantly with imidocloprid toxicity, and direct toxicity due to thiamethoxam poisoning has so far not been documented. This agent has been banned in Europe since 2013 because of its toxic effects on bee colonization and thus an ill effect on cross-pollination.[6] Organophosphates act primarily by inhibition of carboxyl ester hydrolases, particularly acetylcholinesterase thereby preventing degradation of acetylcholine and thus facilitating cholinergic action through continuous activation of muscarinic and nicotinic receptors. Neonicotinoids, on the other hand, act on postsynaptic acetylcholine nicotinic receptors in both the parasympathetic and sympathetic systems. Irreversible linkage of the agents to these receptors initially stimulate, then rapidly block, the Na^+/K^+ channels and inhibit the transmission of nervous influx. The high insect toxicity is because of the predominance of nicotinic receptors in the central nervous system in these species, the absence of the blood–brain barrier, and the specific high-affinity receptor subtypes, particularly $\alpha4\beta2$. In mammals, the predominant receptor subtype is $\alpha4p2$; hence mammals are not affected.[1] However, the breakdown product, desnitro-imidacloprid for imidacloprid and clothianidin for thiamethoxam, either as a result of human metabolism or environmental breakdown, can cross the blood–brain barrier, resulting in effects on humans.[1] The predominant symptoms of toxicity are of neuromuscular weakness and constitutional symptoms (nausea, generalised tiredness and weakness). Plasma concentration of neonicotinoids is not useful in management.

Acute tubular damage due to thiamethoxam is mentioned only in an animal study[7]; it has yet to be reported in humans. Kidneys have α7 nicotinic receptors situated in proximal tubular cells, the stimulation of which has been associated with protection against renal cell injury by induction of heme oxygenase-1 (HO-1) levels via phosphoinositide 3-kinase (PI3K)/Akt and protein kinase C (PKC) signaling, causing decreased secretion of high-mobility group box (HMGB1) protein, with inhibition of α7 nicotinic receptors leading to the opposite action and thus causing

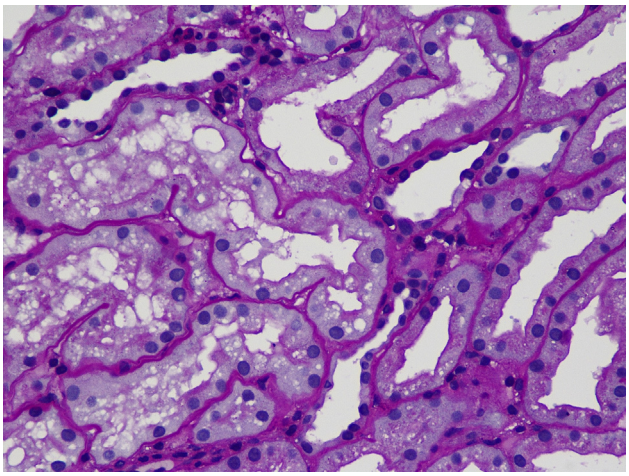

Figure 2. Renal biopsy specimen showing swollen tubular epithelial cells with cytoplasmic vacuoles and mild lymphocytic infiltration in the interstitium (periodic acid–Schiff stain, original magnification ×40).

Table 1. Teaching points

• Acute kidney injury occurs in neonicotinoid poisoning.
• Acute tubular necrosis in thiamethoxam poisoning is possibly due to direct α7 nicotinic receptor inhibition causing proximal tubular injury.
• Supportive care with fluid management and renal replacement therapy, if needed, is sufficient.
• Long-term effects on the renal function need to be studied.

renal tubular injury.[8] Thiamethoxam has been found to have an irreversible inhibitory effect on the α7 nicotinic receptors.[9] Thus it is hypothesized that acute kidney injury in this case is due to direct inhibition of α7 nicotinic receptors in proximal tubules. In our case, the renal biopsy sample showed evidence of acute tubular necrosis, possibly due to a direct toxic effect of thiamethoxam. Furthermore, the hyponatremia and relatively low normal serum potassium in our patient may be due to renal loss secondary to tubular damage.

The increasing incidence of neonicotinoid use for agricultural purposes raises the need for increased recognition of its systemic side effects, one such being acute kidney injury. Table 1 highlights the learning points of this clinical scenario. Early identification and prompt initiation of renal replacement therapy can significantly improve the outcome.

In conclusion, thiamethoxam, a second-generation neonicotinoid, causes acute kidney injury via direct tubular toxicity by a possible mechanism of α7 nicotinic receptor inhibition in the proximal tubule.

DISCLOSURE

All the authors declare no competing interests.

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