Administration of Flumazenil in a Patient with Acute Abamectin Intoxication

Case Report and Review of the Literature

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ABSTRACT

Abamectin is used in several countries as a type of macrocyclic lactone insecticide to control nematodes and other pests in livestock and agriculture. This medicine, used for animals and crops, would be highly toxic to humans if a person has intentional poisoning. We report a case of a 47-year old man who was admitted to the hospital after ingestion of a large dose of abamectin on purpose, and who rapidly recovered consciousness after administration of flumazenil. Although flumazenil is not the antidote of abamectin, we may hypothesize that it could reduce recovery time and shorten expenditures in hospital. This is the first report that focusses on a specific treatment which could possibly accelerate recovery of consciousness for patients with abamectin intoxication.

Keywords: Abamectin, gamma-aminobutyric acid, flumazenil, intoxication, neurological

La Administración de Flumazenil en un Paciente con Intoxicación Aguda con Abamectina: Reporte de Caso y Revisión de la Literatura

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RESUMEN

La abamectina se utiliza en varios países como un tipo de insecticida de las lactonas macrocíclicas, para controlar los nemátodos y otras plagas en la agricultura y la ganadería. Este medicamento, utilizado para los animales y cultivos, sería altamente tóxico para seres humanos que tuvieran la intención de envenenarse. Reportamos el caso de un hombre de 47 años de edad que fue ingresado en el hospital después de la ingestión intencional de una gran dosis de abamectina, y que recuperara rápidamente el sentido después de la administración de flumazenil. Aunque el flumazenil no es el antídoto de la abamectina, podemos asumir la hipótesis de que podría reducir el tiempo de recuperación y reducir los gastos de hospitalización. Este es el primer reporte centrado en un tratamiento específico que posiblemente podría acelerar la recuperación de la conciencia en los pacientes con intoxicación de abamectina.

Palabras claves: Abamectina, ácido gamma-aminobutírico, flumazenil, intoxicación, neurológico

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INTRODUCTION

Abamectin (Avermectin B1) is a type of insecticide used in several countries to control nematodes and other pests in livestock and agriculture. It is a macrocyclic lactone compound that belongs to avermectins, which are fermented from the soil organism *Streptomyces avermitilis* (1).

The mechanism underlying the action of abamectin is its effect on the central nervous system (CNS) of vertebrates and invertebrates. Gamma-aminobutyric acid (GABA) is a very important neurotransmitter that inhibits activation of neurons (2). As a GABA agonist, abamectin has the function of stimulating GABA release from presynaptic inhibitory membranes (3). Other evidence indicates that the action of abamectin is also related to GABA-gated chloride channels; activation of the GABA-gated chloride channel can suppress neuronal activity resulting in ataxia, paralysis and death (4). A negative charge is maintained at the motor neurons as the flux of chloride ions which essentially block transmission between interneuron and excitatory motor neurons (5). In addition, the toxic action of abamectin is also related to the inhibition of mitochondrial activity (6). With the existence of P-glycoproteins in the blood brain barrier, it is difficult for abamectin, under

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therapeutic dose, to penetrate the blood brain barrier. Meanwhile, P-glycoproteins might also explain the selective toxicity of abamectin for parasites over their vertebrate hosts (7).

The mode of action of abamectin and the P-glycoproteins located at the blood brain barrier makes drugs relatively safe in mammals. However, attention has focussed on the neurological toxicity caused by taking this medicine inappropriately (8). Several cases of accidental or intentional abamectin poisoning in humans have been reported (9−12). The effects of abamectin poisoning in humans include coma, myoclonus, polyneuropathy, dilated pupils, partial ptosis and ataxia (10−12). As there is no antidote for abamectin, supportive treatment is the main mode of therapy. The majority of patients who ingest an overdose of abamectin are curable unless the poisoned patient had taken a large dose of abamectin, leading to severe hypotension or respiratory failure which could result in death (13). We report a case of a 47-year old man who ingested a large dose of abamectin on purpose and who recovered his conscious level rapidly after administration of flumazenil.

CASE REPORT

A 47-year old man with diabetes mellitus was admitted to the emergency department (ED) of a local hospital half an hour after having ingested large quantities (200 mL) of abamectin (1.8% active ingredient from emulsifiable concentrate (EC)) with suicidal intent. The claimed quantities were consistent with the empty package that was found. Before this happened, the patient had a quarrel with someone and drank some alcohol. His wife claimed that he did not vomit prior to arrival at the ED of the local hospital. Glasgow coma scale (GCS) of this patient was 13 and gastric lavage and activated charcoal were administrated imme- diately. But the patient gradually went into a coma, so 14 hours after the poisoning, he was transferred to our hospital in Nanjing.

On admission, the patient was in a state of confusion, GCS was 8, blood pressure was 134/78 mmHg, pulse rate was 96 beats/minute, respiratory rate was 18 breaths/minute, and temperature was 37.3 degrees Celsius. He was restless and agitated which made him unable to walk and ataxic on his feet. His pupils were mildly dilated and sluggishly reacted to light. On admission in Nanjing, red blood cell count, electrolytes, liver function, renal function and coagulation function tests were within normal ranges. White blood cell count was 10.7×10^9/L (normal, 4–10×10^9/L) and platelet count was 63×10^9/L (normal, 100–300×10^9/L). He was admitted to the emergency intensive care unit (EICU) after having completed the blood test and chest X-ray. To antagonize the effect of abamectin, 0.4 mg flumazenil was immediately administered once by intravenous injection. The rest of the treatment included small capacity gastric lavage, activated charcoal, aggressive fluid therapy, neurotrophic treatment such as gangliosides and edaravone, protection of the gastric mucosa, *etc*. The consciousness of the patient improved markedly after the therapy of flumazenil. He was fully awake 24 hours after taking abamectin. As GCS of the patient was 15 and he remained stable, he was transferred out of EICU 48 hours after admission. The patient remained haemodynamically and respiratory stable and was discharged from hospital within seven days.

DISCUSSION

We here report a case of a patient with abamectin poisoning who rapidly recovered consciousness from a state of confusion after the administration of flumazenil. There are several case reports of abamectin intoxication in humans (9−12), but none of them involved special treatment. Perhaps this is the first report that focusses on a specific treatment (flumazenil) which could possible accelerate consciousness recovery for patients with abamectin intoxication.

Abamectin poisoning can cause nausea, vomiting, hypotension, coma, myoclonus, polyneuropathy, dilated pupils, partial ptosis and ataxia (10−12). Some of the main symptoms involve the CNS. The symptoms of CNS like confusion, weakness and somnolence were observed during the clinical course of this case and these were consistent with other cases. The clinical severity of abamectin intoxication can be classified into five levels by manifestations (9). In this case, the clinical severity can be assessed as “severe”. Most patients with severe abamectin intoxication develop hypotension but this was not so in this case. Even vasoactive drugs were avoided in this patient. Perhaps this could be attributed to rapid transshipment transfer and timely treatment (gastric lavage, activated charcoal) at the ED of the local hospital. Some researchers have found that hypotension induced by abamectin intoxication may be related to nitric oxide (14) and administration of epinephrine may maintain the normal range of blood pressure *via* nitric oxide regulation (15).

As we described above, there is no special antidote for abamectin intoxication; supportive treatment has been adopted by most clinicians. According to the mode of action of abamectin (3−5), we hypothesized that flumazenil could counteract the action of abamectin at the GABA receptor. There are few reports about administration of flumazenil for humans or livestock with abamectin poisoning. There was a case report of a 13-day old Arabian thoroughbred filly with moxidectin intoxication that improved rapidly with the administration of sarmazenil (16). It is widely believed that moxidectin (belonging to milbemycin) is a widespread antiparasitic drug to several species which share a similar mode of action with abamectin (17), and sarmazenil is a competitive antagonist at the benzodiazepine binding site of the GABAa receptor in the CNS (18). Thus, this case might indicate the benefits of using flumazenil for abamectin intoxication in human beings. However, the cases reported by Chung *et al* (9) showed that the effect of flumazenil may not be significant in patients with abamectin intoxication. But it is important to realize that administration of flumazenil was not the focus of that article.

Furthermore, there is no clear evidence that flumazenil could improve the prognosis of patients with abamectin intoxication. Although the effects of administration of flumazenil

for patients with abamectin intoxication were not obvious, the prognosis of those patients seemed good (9). Some patients with abamectin intoxication, in other cases, were treated successfully with the use of supportive therapy only (10−12). So it is difficult to say that flumazenil could improve the prognosis of patients with abamectin intoxication without more research on this issue. In the index case, the time the patient spent in EICU was 24 hours. Because the clinical data described for patients with abamectin intoxication are rare and incomplete, it is difficult to discuss whether this time in the EICU is short or not. Therefore, more clinical data are needed to settle this issue.

In poisoning cases, laboratory tests of blood, urine or *succus gastricus,* which could confirm the toxicant ingested, are crucial for evaluating the poisoning condition. However, for cases of avermectin poisoning, it is difficult to implement laboratory tests that confirm the concentration of avermectin accurately. For these reasons, we did not detect the concentration of avermectins in this case. Judgment of poisoning severity was dependent on the patient's clinical symptoms and the description by his wife. According to the confession of the patient himself, he ingested large quantities (200 mL) of abamectin and we believe that flumazenil might have played an important role in the recovery of this case.

Although abamectin used in livestock and agriculture is relatively safe for people who ingest it on purpose, there is still the possibility to develop complications like aspiration pneumonia, respiratory failure and even death (9). This report suggests that flumazenil might have potential effects which could promote rapid recovery of consciousness. However, further studies are necessary to confirm this possible effect of flumazenil in antagonizing the action of abamectin and whether flumazenil could reduce recovery time, time in EICU, length of stay in hospital and thus reduce expenditures in hospital.

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