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급성 글루포시네이트 중독 후 서로 다른 예후를 보인 2례: 증례보고

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Two Cases of Acute Glufosinate Ammonium Intoxication with Disparate Outcomes

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초 록

목적

글루포시네이트암모늄은 비선택성 제초제로 1984년 일본에서 개발되었으며, 급성 중독시에는 위장관계 증상뿐만 아니라 의식변화, 경련, 호흡부전 및 기억소실 등과 같은 다양한 임상증상을 보이는 것으로 알려져 있다. 한국에는 1994년 소개된 이후로 널리 사용되고 있으며, 사용량의 증가와함께 음독환자가 점점 증가하여 사회적 문제가 되고 있다. 저자들은 최근 글로포시네이트 중독 환자에서 초기치료 후 지연성 악화를 보였던 2례를 문헌고찰과 함께 보고하고자 한다.

방법 및 결과

첫 번째 증례는 62세의 남자환자로 음주상태에서 글루포시네이트암모늄 음독 후 의식 저하 상태로 발견되어 응급실로 이송되었다. 응급 위세척을 시행 후 보존적 치료 및 집중모니터링을 유지하였고, 의식수준은 6시간 후에 거의 명료한 상태로 호전되었다. 지연성 악화의 가능성에 대해설명하고 지속적인 경과관찰 및 치료를 위해 집중치료실 입원이 필요함에 대해 설명하였으나, 환자와 보호자는 타상급병원으로의 전원을 원하였다. 환자는 이송 중에 발생한 심폐정지로 심폐소생술을 시행하였으나, 회복되지 못하고 사망하였다.

두 번째 증례는 54세의 남자 환자로 글루포시네이트암모늄 음독 후 발생한 의식 변화로 응급실로 이송되었다. 내원시 의식은 혼미한 상태였으며 앞의 증례와 같이 응급 위세척을 시행하였다. 본 환자는 초기치료 후 본원 집중치료실에서 지속적인 혈액 및 생화학적 검사를 시행하였으며, 집중모니터링 및 치료를 유지하였다. 입원 2일째 혈액검사 소견은 호전 중이었으나, 경련이 발생하였으며 의식은 혼미한 상태가 지속되었다. 신경과 협진하여 뇌파검사를 시행 후 항경련제를 증량한 후로 경련은 발생하지 않았다. 입원 7일째에는 의식 수준은 거의 명료한 상태까지 호전되었다. 입원 13일째 혈액 및 생화학검사에서 약간의 혈색소 감소 외에는 정상소견을 보였으며, 뚜렷한 신경학적 합병증 없이 퇴원하였다.

결론

급성 글루포시네이트중독 환자는 매우 다양한 임상증상을 보이며 초기치료 후에 상태가 안정적이더라도 지연성으로 임상적 또는 신경학적 악화가 발생할 가능성이 있으므로 치료에 유의하여야 한다.

Key words: Corpus callosum, Glufosinateammonium

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Introduction

Bialaphos is a non-selective natural herbicide produced by streptomyces viridochromogenes, and was discovered in 1984 by Meiji Seika Kaisha in Japan[2, 6]. The active phytotoxic component in bialaphos is phosphinothricin (PPT), which is an irreversible inhibitor of glutamine synthetase. PPT was first synthesized by Hoechst AG in Frankfurt, and is commonly called glufosinate ammonium (GLA, BASTA®). The clinical manifestations of acute GLA intoxication are unconsciousness, convulsions, amnesia, respiratory failure, nausea, vomiting and hypotension[4-9].

This report describes two cases of acute glufosinate ammonium with disparate outcomes.

Case reports

Case I

62-year-old male was transferred to an emergency room accompanied byhis wife and colleagues. He had a medical history of hypertension and previous stroke. According to his wife, he had consumed about 200ml of glufosinate ammonium herbicide. Chief complaints were not obtained, because his mental status was not clear. His initial vital signs were; blood pressure 130/80mmHg, pulse rate 82 beats per minute, respiration rate 20 breaths per minute, body temperature 38.3℃. The routine biochemistry and complete blood cell count(CBC) were within normal limits, but ammonia was elevated (105 ug/dl, normal range 30-86 ug/dl). Chest X-ray and EKG findings were normal. Arterial blood analysis findings were; pH 7.210, pCO2 37.4 mmHg, pO2 72.7 mmHg, HCO3 14.6 mmol/L, base excess -12.4 mmol/L, and O2 saturation 89.5%. Lactate was elevated at 2.50 mmol/L (normal range 0.5-2mmol/L). The patient had attempted suicide attempt by herbicide ingestion about 30 years previouslyand had fully recovered after gastric lavage.

On this occasion, gastric lavage was also performed (a nasogastric tube had been placed *in situ*on arrived at our hospital), andhe was subsequently kept under close observation in an emergency room. At around 6 hours later and after hydration, his mental status recovered to one of confusion. The patient and his family then refused further evaluation, neuropsychiatric consultation, or admittance to our hospital, and requested transfer to another hospital. Despite being warned of the risksassociated with transfer in the acute stage, they insisted. During transfer to other hospital with emergency medical staff, respiratory arrest occurred, and although cardiopulmonary resuscitation was performed, the patient failed to recover.

Case II

A 54-year-old male was transferred to our emergency room in a stuporous state. He had a medical history of diabetes mellitus and hypertension, andsmall toe of his Rt. foot had been previously amputated due to diabetic foot. He had been diagnosed as having major depressive disorder 1 month before this incidentat a psychiatry clinic, and had maintained his medication for months. At the time of this incident he telephonedhis wife and told her of his suicide attempt, and was later found at home after ingesting around 150 ml of glufosinate ammonium herbicide. Gastric lavage was performed on arrival at our hospital and a nasogastric tube was inserted. His initial vital signs were stable and his blood oxygen level

was normal. Baseline chest X-ray and EKG showed no abnormality. His WBC(white blood cell) count was 19.06 x 1000/mm3, serum creatinine was elevated at 1.79 mg/dl, andinitial arterial blood analysis findings were; pH 7.268, pCO2 31 mmHg, pO2 103 mmHg, HCO3 12.6 mmol/L, base excess -13.0 mmol/L, and O2 saturation 96.8%. Lactate was within the normal range. Several hours after presentation at our hospital, his vital signs became unstable (BP 170/100, pulse rate 114 beats per min, respiration rate 18 breaths per minute, body temperature 38℃)and the patient complained of dizziness. Brain computed tomography was then performed and revealed no significant acute lesion. His respiration rate increased, and thus, we decide on intubation and a continuous infusion of sedative. Mechanical ventilation was performed and he was admitted to the ICU (intensive care unit).

On the second day of admission, generalized tonic-clonic type seizure occurred, but responded promptly to intravenous lorazepam. Laboratory findings were improved, but his mental status remained stuporous, and thus we consulted the neurology department. On the third day, his family requested transfer to another hospital, but when a second seizure occurred in the ambulance they decided against transfer. On the fourth day, EEG (electroencephalography) revealed no epileptiform discharge and moderate cerebral dysfunction, and the dosage of the anticonvulsant Keppra® was 500mg bid to 1000mg bid. On the seventh day, his mentality had improved to a near alert state. Brain magnetic resonance imaging (1.5-TSIEMENS MAGNETOM Avanto, Erlangen, Germany) performed on the 10th day revealed high signal intensity of corpus callosum and posterior commissure on diffusion-weighted images (Fig.1). In addition, laboratory findings were all within normal limits other than a mild hemoglobindecrease, and hewas transferred to a general ward. He was discharged on the 13thdaywithout complication.

Discussion

Glufosinate ammonium (GLA) is a non-selective herbicide and is used as such worldwide [2, 3]. In Korea, GLA was introduced in 1994, and subsequently, its usage increased substantially as it replaced paraquat. The herbicidal action of GLAis related to its inhibition of glutamine synthetase, which is important for ammonia detoxification and amino acidhomeostasis in plants andanimals[1, 2, 10, 11]. Commercial GLA consists of 18.5% GLA and surfactant (sodium polyxyethylenealkylethe rsulfate; AES), and the incidence of GLA intoxication continues to steadily increase. Reported neurological symptoms vary and include mental status change, convulsions, seizures, and amnesia[2, 6, 8].

In animal studies, GLA is known to produce convulsions by stimulating nitric oxide via N-methyl-D-aspartate (NMDA) receptor[12, 13]. Nakaki et al.[14] reported GLA administration increased nitric oxide production in rat cerebellum, and several reports have claimed chronic exposure to GLA induces structural damage in mouse brains, including cerebral cortex, striatum, and hippocampus[8, 15-18]. Furthermore, the AES in BASTA is known to induce nitric oxide production and increase blood vessel permeability leading to body edema, diminished cardiac function, pulmonary edema, and shock.

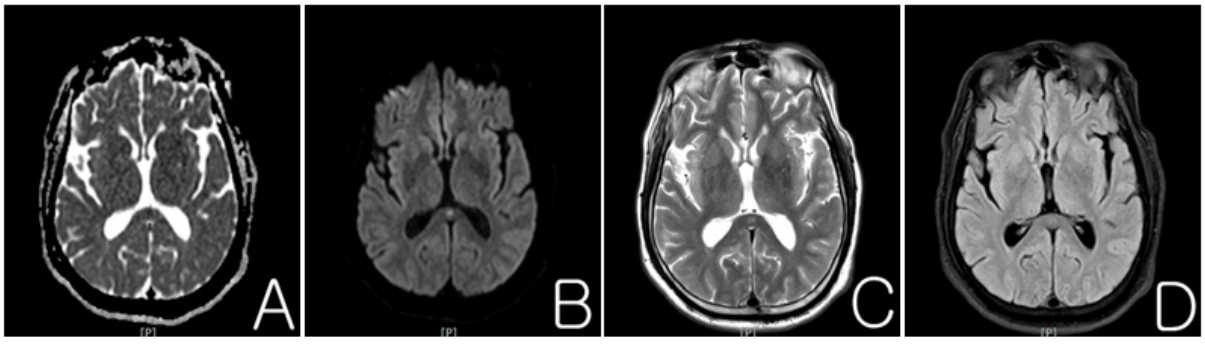
The oral LD50 of GLA in rats is relatively low at 2000mg/kgand acute dermal toxicity (LD50) and inhalation toxicity (LC50) are 1,380mg/kg and 3.22mg/l, respectively, for an

exposure time of 4 hours[19, 20]. The acute oral toxicity of GLA in man is 1.6 to 1.8ml/kg[20]. Pure GLA is less toxic to mammals than plants because its ability to cross the blood brain barrier and glial cells is limited by its high polarity. However, the internal absorption rate of GLA in the presence of AES is 25-30% higher than for GLA alone, and thus, even small doses of BASTA can affect the central nervous system[4].

Our patients both ingested volumesthat exceeded the acute oral toxicity of GLA. The patient that ingested ~200cc of GLA went into cardiac arrest, and the other conservatively ingested about 150cc experiencedneurological deterioration. At arrival, both exhibited slight respiratory rate elevation, fever, and metabolic acidosis, and moderate neurological symptoms. However, clinical and neurological symptoms and signs deteriorated rapidly over the first 24 hrs of hospitalization, and eventually, one of the two expired after cardiacarrest. A report issued by Hirose et al. [21]on GLA intoxication mentioned delayed onset of central nervous systemsymptoms, convulsion with cyanosis, fever, and high blood pressure after 23 hours, which cautions medical staff to be aware of delayed symptoms and signs in GLA intoxication cases.

The hippocampus contains the highest density of NMDA receptor in the rat brain, where they play a crucial role in spatial memory and memory acquisition. Mice chronically treated with GLA were reported to spent more time than controls in the Elevated Plus-Maze (EPM) test, indicating hippocampal deficiency, but to have normal locomotoractivities[17]. Youn et al.[8] reported anterograde amnesia and a lesion of bilateral hippocampus as determined by MRI in male patientand Oh et al.[16] reported a case of bilateral basal ganglia lesionin male patient after GLA intoxication.Brain imaging studies in mouse revealed signal abnormalities usually occur in hippocampus after GLA intoxication[18]. And the activity of glutamine synthetase inhibition significantly increased in the hippocampus mouse treated with GLA[18]. MRI findings of Case II revealedhigh signal intensity in posterior corpus callosum. A transient splenial lesion in the corpus callosumobserved 6 daysafter GLA ingestion, was also reported to have spontaneously disappeared four weeks later[15].

Figure 1.



Brain magnetic resonanceimages of Case IIon hospital day 11. Apparent diffusion coefficient (ADC) image showing a focal low signal intensity lesion was observed in the splenium of the corpus callosum(A). The lesion corresponded to a region of subtle high signal intensity on this diffusion weighted image(B). T2-weighted(C) and fluidattenuated inversion recovery(D) imagesof the same lesion.

Conclusion

Acute glufosinate ammonium intoxication has varied clinical features and outcomes, as demonstrate by this case report. Despite a stable initial state, delayed deteriorations of clinical and/or neurological manifestations can occur and lead to death. Cases of GLA intoxication should be properly managed after prompt and accurate diagnosis.

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