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A Case of Niclofolan (Bilevon®) Intoxication

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INTRODUCTION

Niclofolan(menichlopholan; 5.5′-dichloro-2, 2′-dihydroxy-3, 3′-dinitro-biphenyl) was once tried as a chemotherapeutic agent against *Clonorchis sinensis* infection. And it had been expected to be an excellent drug by its wormicidal effect when dosed 1.0mg/kg for 3 times or 2.0mg/kg for 2 times(Rim, 1975; Soh *et* Im, 1977; Rim *et* Lee, 1979). The worms expelled by niclofolan were damaged seriously of their reproductive organs, and the parenchyme and digestive organs were observed to be hyalinized(Rim *et* Lee, 1979).

However, most of the treated cases complained severe ischiosacral neuralgia, myalgia of extremities, sweating and other nonspecific symptoms after administration of niclofolan. As much as 97.1% out of the treated(Rim *et* Lee, 1979) complained of adverse reactions. These severe and frequent toxic reactions made this drug be abortive in wide use.

However, because of public demand, some clinicians or pharmacists used to recommend niclofolan to the patient of clonorchiasis because there had been no other choice for it in Korea. The drug was imported primarily for veterinary use in controlling fascioliasis of cattle. Therefore, there was not any available instruction for use against human clonorchiasis in the package of the drug. The authors observed a case of incidental niclofolan intoxication by overdose occurred in such context, and followed the clinical course of toxic manifestations.

CASE RECORD

A 15-year-old Korean middle schoolboy, who complained of vomiting and dizziness, was admitted to Department of Pediatrics, Seoul National University Hospital(SNUH) through Emergency Room on August 25, 1981.

The patient was announced to be infected by *Clonorchis sinensis* through the biannual fecal examination of students executed by the Korean Association for Parasite Eradication in July, 1981. The boy resided in Seoul, and had a history of intake of fresh water fish at Asanman, Gyeonggi Do in the summer of 1980. After confirming the infection at a hospital near home, the boy began to take niclofolan(Bilevon®) 43 mg(1mg/kg) in a dose, which was obtained from a nearby drugstore. After several doses, he felt headache and dizziness, but he was encouraged to take more. When the boy had taken total 473mg of niclofolan in 11 divided doses every other day for 20 days until August 23, 1981, sudden attack of vomiting, severe dizziness and visual disturbance occurred. The drug was discontinued immediately, though 15 doses were originally scheduled. The symptoms aggravated day by day and excessive sweating appeared on August 25. The patient visited a nearby hospital and then transferred to SNUH.

By physical examination on admission, liver tip was palpated and mild yellowish discoloration of skin and sclera was noted. By blood chemistry,

the value of serum enzymes, GOT/GPT increased to 91/54 IU per 100ml (normal range, 0-16/1-16 IU per 100ml). The patient was managed with general supportive measures under the impression of toxic hepatitis by niclofolan. Visual disturbance persisted. And severe ocular pain developed after admission. Headache and dizziness were not controlled and severe enough to hamper sleeping. On August 27, funduscopy revealed blurred optic disc margins of both eyes. The boy began to complain shoulder pain on August 30 and it disappeared on the next day together with excessive sweating. However, in the morning of September 1, there happened an episode of seizure attack combined with eyeball deviation for 2 to 3 minutes. The intracranial pressure was over 30 cm H_2O when checked after the attack. Mannitol and glycerol were administered to control the increased pressure, which sustained for later two months. Brain CT scan showed normal shadows. The consciousness of the case was clear and well oriented during the whole hospitalization period. Furuncles on face and skin eruptions on trunk appeared transiently probably due to drug eruption for a week in September. Obvious papilledema and flame-shaped retinal hemorrhage were observed on September 14 and lasted until September 30. The elevated levels of serum enzymes settled in normal range after September 7. The body weight was 43kg before this illness. But it decreased to minimum 34kg during hospitalization. This was probably due to persistent vomiting. The weight regained over 40kg after early November, 1981.

The boy was discharged on October 2 from the hospital and followed at Out Patient Clinic of SNUH. He revisited Emergency Room due to headache, nausea and vomiting on October 13, two days after stop of glycerol administration. These problems were controlled by readministration of glycerol. The sustained problems such as hepatomegaly, increased intracranial pressure and papilledema disappeared at the end of October. However, headache, dizziness, ocular pain and visual disturbance developed intermittently, until December, 1981, about 4 months after the onset. Thereafter, by the weekly observation of the case, no clinical problems related with this episode has been noted until March, 1982.

DISCUSSION

The clinical problems of present case were divided into two categories; one from toxic hepatitis and the other from increased intracranial pressure. The symptoms and signs from hepatotoxic effect were mild jaundice, general weakness, hepatomegaly and increased serum transaminases. These were not so severe generally. The liver problems of the case disappeared after one month. However, the clinical manifestations of increased intracranial pressure, such as headache, nausea, vomiting, blurred vision, ocular pain, papilledema and retinal hemorrhage, were very severe and intractable. These persisted about two months. Other than these categories, there were shoulder pain and sweating. These subsided within a week, and supposed as manifestations of neurotoxic reaction.

By an unpublished document, niclofolan was toxic to liver, kidney and brain. And the animals dosed 3.0mg/kg were euthanized after 6th or 7th administration. When dosed 1.0mg/kg chronically, the drug was proved to induce vacuolization in brain cortex mainly by edema formation. There found growth retardation, too. The toxic effects of niclofolan were said to develop dose-dependently in that document. These experimental findings explained well the clinical manifestations of present case. However,

there still remained a question how could the boy endure the toxicity of drug until the 11th dose of total 473mg(11mg/kg) which was over-dosed about 3 times of conventional dose. It might depend upon small amount(1mg/kg) of a dose and the interval of 48 hours between each dose.

By the report of Rim *et* Lee(1979), it was always toxic when niclofolan was used in therapeutic dose. And when used in non-toxic dose (0.5mg/kg, 2~3 times), wormicidal effect was far beyond satisfaction in clonorchiasis. Therapeutic dose of niclofolan is total 3~4mg/kg and lethal dose is about 18mg/kg by above mentioned unpublished experiment. Therefore, its safety margin is too narrow to be recommended as a chemotherapeutic for *Clonorchis* infection. When a drug is widely used in public, the possibility of overdose always ambushes. Especially such event as present case can occur not uncommonly in the society of free marketing system of drugs like Korea. Present case should be the last victim of overdose intoxication of niclofolan. And from now the safer drug, praziquantel(Rim *et al.*, 1981) should be recommended to clonorchiasis patients.

SUMMARY

The authors reported a case of niclofolan intoxication occurred during the trial of clonorchiasis treatment. The case, a 15 years old Korean schoolboy, took niclofolan (Bilevon®) of total 473mg(11mg/kg) in 11 divided doses during 20 days. And the case suffered from neurologic symptoms such as severe headache, dizziness, nausea, vomiting, blurred vision, papilledema, retinal hemorrhage, an episode of seizure attack and elevated intracranial pressure, and hepatotoxic symptoms such as hepatomegaly, increased serum transaminases, and shoulder pain, excessive sweating and weight loss. Therapy was concentrated to the management of the elevated intracranial pressure. Hepatotoxic manifestations subsided within one month. The clinical signs related to elevated intracranial pressure persisted two months. Body weight regained after 2 months. And the symptoms of headache, dizziness and vomiting were complained intermittently until 4 months after onset. However, no subsequent clinical problems related with this episode has been noted until this record.

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=국문초록=

Niclofolan(Bilevon®) 중독증 1례

서울대학교 의과대학 기생충학교실 및 소아과학교실
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Niclofolan은 1970년대 후반에 肝吸蟲에 대한 殺蟲효과가 우수하다 하여 치료제로 시도되었으나, 毒性이 매우 강하고, 복용자 중에서 부작용을 호소하는 비율이 매우 높아, 실제 치료에는 쓰이지 못하고 사용이 중단된 약제이다. 최근까지 肝吸蟲에 대한 치료약제가 마땅하지 않아, 간혹 病醫院이나 약국에서 Nicofolan(Bilevon®)을 투여하는 경우가 있었는 바, 著者들은 過用에 의한 중독例를 경험하여 그 경과를 관찰하였다.

환자는 서울에 거주하는 15세 남자 중학생으로, 1981년 春季 學生檢便에서 肝吸蟲卵 양성자로 판명되어, 이를 치료하고자 서울 시내의 한 약국에서 Niclofolan(Bilevon®)을 20일 동안 격일로 1회 43mg씩(1mg/kg의 용량) 총 11회에 걸쳐 473mg을 복용하였다. 11번째 복용후 갑자기 두통, 현기증, 구토, 시력장애등의 증상이 나타나고, 이어 심한 發汗과 어깨의 통증이 동반되어 1981년 7월 25일 응급실을 통해 서울대학교병원 소아과에 입원하였다.

입원당시 약한 황달현상이 보였고, 간의 끝이 만져졌다. 간기능검사에서는 혈청 GOT/GPT값이 91/54 IU로 증가해 있었다. 또한 眼底검사를 통해 視神經 乳頭의 울혈과 眼底出血이 관찰되었다. 發汗과 어깨의 통증은 發病 1주 이내에 사라졌으나, 9월 1일에 전신 경련이 2~3분동안 한 번 있었다. 경련 직후 뇌압이 30cm H_2O이상으로 증가된 것으로 측정되어 mannitol과 glycerol로 치료를 받았다. 간기능의 이상은 입원 1달 후에 정상으로 회복되었고 10월 2일 퇴원한 이후 외래에서 관찰하여 뇌압상승과 시신경울혈은 發病 2개월 후에야 회복되었다. 입원후에 34~35kg까지 줄었던 체중도 11월에서야 40kg이상으로 회복되었다.

두통, 현기증, 시력장애등을 가끔 호소하였으나 12월 이후에는 임상적으로 완전히 회복되었다.