

TREATMENT OF ACUTE YELLOW ATROPHY OF THE LIVER WITH PARAOXYBENZOIC ACID

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Mizuta and his associates¹⁾²⁾³⁾ have previously demonstrated that either in the urine of the normal man or in the blood of the patients of kidney diseases, there exists a powerful substance capable of promoting the liver functions, and named it "Hepatotropin". Further investigation by Inagaki⁴⁾ revealed that some of the aromatic fatty acids also show a similar action accelerating the functions of the liver. Of these compounds, hippuric acid and paraoxybenzoic acid were suggested by Hoshino⁵⁾ to be useful as chemical agents for clinical treatment of hepatic diseases.

For the recent few years, our clinic has been studying the hepatotonic action of "calcium paraoxybenzoicum", abbreviated as "POB", and has so far demonstrated that this compound markedly promotes the excreting and detoxifying functions of the liver. Experimental studies in rabbits revealed that the phosphorus poisoned animals which otherwise die are able to survive the poisoning when this drug is administered. Clinically, it is expected that the effect of a hepatotonicum might be manifested most clearly as a decrease in the mortality rate in serious hepatic disturbances to which the drug is applied. As such hepatic disturbances, we took up acute yellow atrophy of the liver showing a high mortality rate with a shorter course. The present paper describes four cases of serious acute yellow atrophy of the liver, all of which have been cured by treatment with our hepatotonicum, "POB".

REPORT OF CASES

Case 1.—K. H., a 25 year old man, first seen and admitted to the hospital on Dec. 25, 1948. He had been treated by a physician as a case of jaundice for two weeks, having a poor appetite. Three days before admission there developed a serious headache and nausea, and occasionally he became somnolent. He had had no sensation of fever or abdominal pain, and had been unable to take anything but soda-water.

Physical examination.—The patient was a moderately developed and nourished man, being soporose but able to reply to what questioned. He had a pronounced jaundice, but not injected conjunctivae or hemorrhage in the skin and mucous membrane. The pulse was normal and numbered 80. A tender, somewhat firm liver was palpated three fingerbreadths below the right costal margin.

Laboratory findings.—On the fourth day after admission, the blood examination showed 13200 white blood cells, with 71 per cent neutrophils, the majority of which being polymorphonuclears with no demonstrable nuclear degeneration, a prolonged bleeding time of 23 minutes, and a normal coagulation time. The van den Bergh test revealed a delayed direct and a positive indirect reaction, the Meulengracht's icterus index was 220, and the reaction to the Wassermann test was negative. The urine was negative for albumin, sugar, urobilinogen and leucine crystals, and positive for the Gmelin test, hyaline, granular casts and tyrosine crystals.

Course and treatment.—This case was diagnosed from the foregoing data as cholemia resulted from acute yellow atrophy of the liver, and was given intravenously 20 ml of 3 per cent "POB" solution two times a day since the next day of admission for eleven days. The Ringer solution, glucose solution, vitamin B complex and heart remedies were also administered additionally when necessary. The cerebral symptoms which had been manifest since three days before became profound since the next day of admission with coma, delirium, incontinence of the urine, and gingival bleedings. With the treatment, the patient spontaneously recovered from unconsciousness on the sixth hospital day, and became mentally normal within a day. Thus getting out of the danger on the fifth day of the "POB" treatment, he gained appetite and general improvement, though he complained of epigastric pain which required an injection of morphine on the seventh day. The icterus index was lowered to 126; but since about 19 days after admission the patient developed demonstrable ascites, and thereafter abdominal taps were necessitated every three or four days. The definitely positive Takata-Jetzler test (precipitation in 10 tubes) and cobalt test (8 tubes) suggested the development of cirrhosis. On the 32nd day after admission, Talma's operation was performed with resumption of the "POB" therapy, and biopsy of the liver was done simultaneously which was observed grossly to be cirrhotic and enlarged for two fingerbreadths below the costal margin by operation. Ever since the operation was done, the paracentesis was never required (Umber and others have recommended the simple laparotomy for such a case), and the patient left the hospital in a perfect condition 60 days after admission. Follow-up studies revealed that he has been capable of heavy works since half a year after being discharged from the hospital.

Biopsy findings.—The specimen was taken 45 days after the onset of jaundice and 35 days after the occurrence of cholemia. Pronounced perilobular overgrowth of the connective-tissue with a few lymphocytes, and atrophied acini with disarranged liver cords and intra-lobular fibrosis were observed. The parenchymal cells were almost normal except for a few including intra-cellular vacuoles, and there was seen compensatory hypertrophy of the parenchymal cells with a greater number of binucleated cells. In short, the microscopic findings suggested previous and serious destruction of the liver cells, and the case was presumed to have developed secondary cirrhosis following acute yellow atrophy of the liver.

Case 2.—K. N., a wife 34 years of age, was admitted to the hospital on March 10, 1950. A detailed history revealed nothing worthy of comment. She had had languor, and occasionally chills with fever for about a month. She got aware of jaundice 20 days prior to admission, which was then accompanied with aggravating anorexia and constipation. The sleep was disturbed by severe headache and vomiting had developed 4 to 5 days before admission. She, who was in eight weeks' gestation at the time, had a genital bleeding of a small amount shortly before admission. Later, she had an artificial abortion.

Physical examination.—Physique, normal; condition of nutrition, good; consciousness, almost normal; pulse, normal with a rate of 85; temperature, 37.2°C. —remaining thereabout through the whole course; icterus of high grade, without pericorneal injection; liver, palpable for two fingerbreadths below the costal margin, and somewhat soft and tender upon pressure; knee jerk, diminished; no abnormal reflex.

Laboratory findings.—Examination made the next day revealed: 13200 white blood cells (82 per cent neutrophils, chiefly polymorphonuclears); 140 icterus index; positive direct and indirect van den Bergh reactions; positive Takata reaction (5 tubes); and negative reaction to the Wassermann test. The urinalysis: albumin, negative; sugar, negative; urobilinogen, negative; Gmelin test, positive; white and red blood cells, 1 plus each; casts, and crystals of tyrosine and leucine, negative.

Course and treatment.—The patient became restless and irritable soon after admission, and did not sleep the night. This condition was intensified the following day, and the patient became comatose with urinary incontinence, sometimes uneasy crying on account of headache. This was considered an evidence of cholemia, toward which "POB" (20 ml of 3 per cent solution) was given three times a day, with supplementary addition of the Ringer solution, glucose solution, vitamin B complex, etc. Yet, the unconscious state was still worsened, the patient sometimes complaining of thirst, singing folk-songs loudly, and refusing to eat. This grave state continued until seven days after admission, when the patient began regaining consciousness. On the ninth hospital day, she was quite normal mentally, had some appetite and no incontinence of the urine any more, the injection of "POB" being then reduced to twice a day. During the episode of unconsciousness, the signs of nervous involvement, such as Kernig's sign, stiff neck, motility disturbance and abnormal reflex, were absent, and the cerebrospinal fluid was normal. The liver which had been palpated for two fingerbreadths at the first examination was diminished and impalpable ten days after admission. The icterus became less apparent, but ascites more conspicuous instead. High protein regimen containing cow liver was then administered together with "POB" and vitamin B complex. Three paracenteses were required during the ensuing ten days, and thereafter no ascites could be proved. The Takata-Jetzler reaction was still strongly positive (10

tubes), but the excretion of dye (Azorubin S) was normal. The patient was discharged thoroughly cured 50 days after admission, and is quite healthy at present.

Case 3.—T. F., an unmarried woman aged 27, company employee, was first seen on July 5, 1950. Her previous history was noncontributory except pyelitis she had had in March. She had had malaise, headache, irregular fever ranging from 37.5° to 38.5°C, and inappetence since June 24. Sulfathiazole was given 4 gm a day for two days beginning June 26 by a physician for the clinical findings of pyelitis, but was suspended for a development of vomiting. Although the fever subsided, she had a very poor appetite and developed manifest jaundice and vaginal bleedings after July 1. These symptoms then rapidly intensified, she became comatose and required catheterization for urinary retention three days after the onset of icterus. An ample amount of fluid, including glucose, insulin, and vitamin B complex and K, etc. were given.

Physical examination.—The patient was first examined three days after the onset of cholemia: physique and nutrition, good; comatose, and not reacting to questions; temperature, 38.6°C.; pulse, 80 per minute and good tensed; marked jaundice with miliary to pinhead sized subcutaneous hemorrhage and gingival bleeding; no pericorneal injection; systolic murmurs at the base of the heart, and accentuation of the second pulmonic sound; liver, palpable for two fingerbreadths on the mammillary line below the costal margin, somewhat hard and tender; spleen, impalpable; tendon reflexes, diminished; no abnormalities of reflex or motility.

Laboratory findings.—The urinalysis disclosed: a trace of albumin; sugar, negative; urobilinogen, weakly positive; Gmelin, positive; red blood cells, white blood cells, bacilli and epithelial cells, positive; casts and crystals of tyrosine and leucine, negative.

Course and treatment.—The treatment with "POB" was initiated in place of the previous insulin therapy two days after onset of cholemia (the day before the first examination), administering 20 ml. two or three times per day. The unconscious state continued until the fifth day of cholemia (July 7), when she was awakened, able to reply to what questioned and urinated voluntarily, thus recovering from the crisis. The examination made shortly before the awakening revealed: no particular change in the blood picture; icterus index, 55; positive Takata-Jetzler test (8 tubes); and negative Wassermann test. The liver which was impalpable during the coma period, was palpated two fingerbreadths and soft. There developed no demonstrable ascites during the whole course. "POB" was given for ten days to this case. The follow-up made three months later disclosed a negative Takata reaction, and the liver of the same size. The patient has since been in a perfect condition of health.

Case 4.—T. B., 32 year old woman, took "Nekoirazu," a ratsbane, for the purpose of suicide on the evening of Mar. 4, 1951. "Nekoirazu," which contains 8 per cent phosphorus, is one of the rat poisons popular throughout Japan, and

has often been resorted to for this extraordinary intention. The lethal dose is 2 to 5 gm, and if taken, there develop fatty degeneration of the liver from 3 to 4 days later, and eventually insufficiency of the liver and cholemia, which result in death in 8 to 10 days. There have been only few cases, if any, that survived this poisoning. She was found irritated and complaining of epigastric pains two hours after the attempt, and was hospitalized immediately.

Physical examination and course.—Physical examination revealed a moderately developed, well nourished woman; she was restless; and the liver was palpable for one and a half fingerbreadths below the costal margin, and soft. Immediate gastric lavage was carried out on admission, and an ample amount of glucose solution and vitamin B complex were then given. On the third day of the illness, the bromsulfalein test was 25 per cent even at 60 minutes, the icterus index was 13, and the Takata test was positive; on the fifth day, the bromsulfalein test was 60 per cent at 60 minutes, the Takata test was definitely positive (7 tubes), the icterus index was 20, and a manifest jaundice was observed. She was sleepless due to frequent vomitings. The "POB" therapy was launched on the fourth day of the illness, with a dose of 20 ml. two times a day, which resulted in a gradual improvement of the general condition beginning the third day of the treatment, with subsequent negative turn of the Gmelin test and urobilinogen in the urine, thus enabling us to terminate the treatment after six days administration. The icterus index was reduced to 9 fourteen days after admission, and soon later the hippuric acid synthesis test and the bromsulfalein test turned to normal. The follow-up was quite satisfactory.

CONCLUSION

The present report is based on three cases of idiopathic acute yellow atrophy of the liver whose cause was unknown, and one case of the same disease caused by phosphorus poisoning. The parenteral administration of "calcium paraoxybenzoicum (POB)," a new hepatotonicum, was the principal procedure of the entire treatment, which was also reinforced with an appropriate combination of other supplements such as glucose solution, Ringer solution, vitamin B complex, etc. Serious cholemia which developed in the three idiopathic cases, subsided by degrees from the third to the fifth day of the treatment, with restoration of consciousness and improvement of the general conditions. Though two of the three later developed cirrhosis of the liver — the one received Talma's operation (biopsy was done) and the other was given high protein diet while receiving "POB" — both were cured in a relatively short period.

This disease is widely recognized to be serious in its prognosis, the fatality rate being more than 70 per cent, with rare survivors. The fact that the four consecutive severe cases of this disease were successfully treated, is difficult to consider to be an accidental occurrence, without taking into consideration the

beneficial effects of "POB." The authors are of the opinion, from the data of their experimental and clinical studies, that "POB" was the very factor with which the aforementioned results can be explained.

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