TOXIC HEPATITIS DUE TO CINCHOPHEN

A REPORT OF THREE CASES

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Cinchophen or atophan (chemically 2 phenyl-quinoline 4 carboxylic acid) was first prepared by Doebner and Gieske[1] in 1887. It was introduced by Nicolaier and Dohrn[2] in 1908 for the treatment of gout. The tenth edition of the U.S.P.[3] recognizes it as cinchophen. It was generally considered that the drug was of low toxicity; Sollman[4] gives no warning against long continued massive dosage; the general practice has been to maintain saturation over long periods.

However, as early as 1913 cases of skin rashes and gastro-intestinal upsets resulting from the use of this drug were reported in the literature. [5] [6] In 1922 Schroeder[7] drew attention to the toxic effects of the drug, and published a review of 17 cases in which such effects were observed. In 1927 Reichle[8] reviewed 47 cases collected from the literature among whom 11 patients had died from toxic jaundice.

Because of these toxic effects, it seems worthwhile to offer a discussion of some of the more common symptoms produced by this drug, and to present three cases of toxic hepatitis due to its use, one of which was fatal.

Cinchophen is a white powder having a sour and bitter taste. It is related chemically both to the alkaloids and acids. It is acid in reaction and forms salts with the alkali metals.[9] It has been used with excellent results in the treatment of gout and allied conditions, its action closely resembling that of the salicylates. It is also effective as an analgesic antipyretic, and promotes the excretion of uric acid by direct action on the kidneys. This last effect is thought to be due to an increased permeability of the kidney to urates, so that those previously retained in the blood because of the difficulty attending their elimination by the kidney escape in the urine.[4]

The absorption of cinchophen from the stomach occurs very promptly. Its effect on the excretion of uric acid is at its maximum about an hour after the drug has been given by mouth, the effect beginning to decline in three hours. This is a temporary effect, however, as although the excretion of uric acid is increased during the first three days of administration of the drug it then returns to normal, or below, whether administration of the drug is continued or not. For this reason many recommend that the drug be given for periods not exceeding three days, and that it then be discontinued

for at least four days. For the most part the drug appears to undergo decomposition in the tissues, although an unchanged portion is excreted in the urine.[10] Almost every case of poisoning which has been reported was the result of uninterrupted use of the drug over long periods of time.

In medicinal doses cinchophen usually causes no symptoms whatever. In very large doses it may cause a burning in the stomach which lasts only a short time.[9] The toxic action of the drug is thought to be due to the presence of the quinolin nucleus, which consists of the benzene and pyridin rings.[4] Most individuals are not susceptible to the toxic action, and toxic jaundice occurs only in the presence of an individual idiosyncrasy, which may be artificially induced. For this reason a therapeutic test of the drug before its administration has been advocated. The dosage and the duration of administration before the onset of symptoms varies with the individual case.[11] Cases of extreme toxicity have been reported following very small doses.[11] The symptoms come on abruptly, and, as a rule, appear late. Frequently they may appear some time after administration of the drug has been stopped. The amount of glycogen present in the liver is probably an important factor in the production of toxicity, there being a greater tendency to liver degeneration when this amount is small. Thus, alcoholics, pregnant women, and those who have previously suffered from liver disease associated with jaundice are more likely to suffer the toxic effects of administration of cinchophen. The route of attack is not definitely known.[11 12]

The principal symptoms of toxicity due to cinchophen are headache, gastrointestinal disturbances, and jaundice. The most frequent of these is jaundice, which has been present in almost every reported case. Vomiting, anorexia, heartburn and diarrhoea, when present, usually precede the jaundice. On the other hand, jaundice may appear first and be intense from the beginning and it may be accompanied by diarrhoea.[13] Weakness may be noted first, and in some cases this symptom has been accompanied by emotional disturbances and loss of voice.[14] Itching of the skin is a common symptom.[15]

As a rule the first symptoms noted are pains in the right upper quadrant and right back, and vomiting. After the patient has felt ill and tired for a few days, jaundice sets in. Severe vomiting, often of a bilious nature, may be present from the outset. Sleepiness and stupor progressing to delirium frequently occur, and the patients rapidly retrogress, the majority dying in coma.

The liver may at first be enlarged, but soon begins to decrease in size until it cannot be felt. As a rule, the left lobe decreases more rapidly, and this is an important point in diagnosis. The jaundice is very rapid in its development and varies in its intensity. The spleen, although it is enlarged, can seldom be felt.

The amount of urine decreases. It is dark brown and contains traces of albumin but no sugar. Hyaline and granular casts, red blood cells and bilirubin crystals may be found. Tyrosin may be present but is not of diagnostic significance. The total nitrogen of the urine is increased, as are also the ammonia and uric acid. The duodenal contents may or may not show bile. The patients are usually constipated; the stools may be acholic and at other times may show bile. The blood shows a markedly increased bilirubin. The blood sugar is first increased and later decreased. The sugar tolerance is later decreased. Blood coagulation is decreased and the bleeding time increases early. The red blood cells and hemoglobin are usually increased, although the former may be markedly decreased. The total number of white blood cells is usually increased, but leukopenia with relative lymphocytosis may occur. The temperature is variable; there is a high rise before death.

The duration of the symptoms varies with the severity of the process. It is important to remember that these cases may present symptoms of acute gall bladder disease, and there are cases on record in which an operation has been performed.[12]

Early diagnosis is important. At the first sign of toxicity the administration of the drug should be stopped, and a careful watch kept over the patient. If urticaria occurs calcium lactate may be used. For the relief of the gastrointestinal symptoms glucose should be given in large amounts, by mouth, in the form of the Murphy Drip, or intravenously, if the symptoms are at all severe. When glucose is administered insulin should be given also in order to better fix the glycogen of the liver to protect it from further damage, and so to aid in recuperation of this organ.

The pathological picture resembles that of acute yellow atrophy. The liver is small, and the left lobe may be so atrophied as to have almost disappeared. There is almost complete necrosis of the liver cells with little or no evidence of regeneration. The bile ducts are unaffected. The kidneys are large, soft and pale. The damage is chiefly in the tubules of the cortex, and is in the nature of cloudy swelling and destruction. The glomeruli apparently escape damage, and the collecting tubules are normal. As a rule other organs are not affected, although cases have been reported in which there were

present acute splenic hyperplasia,[8] acute pancreatitis[16] and petechial hemorrhages on the mitral valves, pleura and mucous membranes of the stomach and jejunum.

During the past fourteen months three cases of toxic hepatitis due to cinchophen have been seen at the Cleveland Clinic; one of these was fatal. The case reports follow:

Case 1.— The patient, a man 45 years of age, was first seen at the Clinic on October 16, 1929. At that time he complained of pain in the left hip and back, which had been present for several months, and which was so severe as to incapacitate him. The pain had been growing worse recently, and the patient noted that it was aggravated by cold and rainy weather. At first it was worse in the evening and better in the morning, but recently the patient had noted stiffness in the joints on waking in the morning, with some limbering up on motion. The family and personal history were unimportant.

The patient was a very robust, rather obese man, weighing 210 pounds. The temperature was 98.6°, pulse 80, blood pressure 152/88. There was a scoliosis to the right in the lower two-thirds of the dorsal spine, and to the left in the lumbar spine. He moved with great difficulty. There was a marked restriction of movement in all directions in the lower back. There was marked tenderness over the right flank, at which point no masses could be discovered. There were no gross changes suggestive of polyarthritis. There were extensive varicosities over the right saphenous vein to a point two inches above the knee. There was extensive pyorrheal involvement of the teeth. The patient experienced discomfort on straight leg raising on both sides, particularly the right.

At the time of this first examination the impression was gained that the patient had a hypertrophic arthritis aggravated by his activity, and that the present acute attack was due to an injury superimposed on the arthritic process.

Examination of the nose and throat showed a deviation of the nasal septum to the left and chronic tonsillitis, indicating that the tonsils might be a focus of infection.

X-ray examination revealed a marked left lumbar and lower dorsal scoliosis with rotation, with considerable hypertrophic arthritis.

The diagnosis made at this time included scoliosis, hypertrophic arthritis of the spine, chronic tonsilitis, and pyorrhoea.

The patient was advised to rest, to apply heat to his back, to have the teeth cared for and to have tonsillectomy if no improvement resulted from these measures.

On October 21st he reported that he felt much better, but on January 6th the patient's wife reported that the symptoms had increased in severity and she was advised to bring him to the hospital.

The patient was seen on January 13th, when he stated that he had been having very persistent pain in the lower back and upper spine. He had been taking cinchophen for several days, but the exact amount administered was not known. He had had some gastrointestinal disturbance and about January 8th jaundice had developed accompanied by considerable nausea and some pain in the right upper quadrant of the abdomen.

Examination at this time showed a diffuse icterus, with a yellowish discoloration of the sclera. Movement in the lumbo-sacral region was markedly restricted and there was tenderness over the lower back. The liver edge was palpable and tender.

The patient was referred to the Medical Division for further investigation, and the following additional history was obtained. Six days before this visit he had had mild pain in the epigastric region, accompanied by nausea and vomiting. The skin became yellow. The urine was highly colored and the stools were pale in color. The pain lasted for some hours and then was relieved. The stools continued to be pale in color. The impression at this time — January 13th — was that there was an obstruction of the common duct or catarrhal jaundice.

The patient was admitted to hospital on this date. Further examination in the hospital disclosed marked jaundice with red palms and finger tips. There were numerous telangiectases in the skin. The chest was barrel shaped with prominence on the right side posteriorly and flattening on the left side. Percussion and auscultation gave normal findings. The abdomen was evenly rounded with a slightly full contour. The liver was palpable at the right costal margin and was not tender. There was some tenderness to pressure in the region of the right costal margin and also at the tip of the eighth left costal cartilage. The temperature was 99.4°, pulse 70, respiration 20, blood pressure 112/60. An x-ray examination of the gastrointestinal tract made on January 15th disclosed a nonfunctioning gall bladder. The serum bilirubin on the day of admission was 16.7 mg. per 100 c.c. Blood count: red cells 4,370,000; white cells 5000; hemoglobin 80; polymorphonuclears 72, small lymphocytes 20, large lymphocytes 8. The urine contained albumin 1+, bile 2+, and there was an occasional hyalin and granular cast.

On January 23rd the patient's condition was about the same. The jaundice was quite deep; serum bilirubin was 22.7 Some distress was present over the chest and up into the neck. The liver was palpable, regular in outline and not tender. On January 29th the patient did not feel at all well. There was a feeling of tightness across the lower chest and axillary regions, particularly on deep inspiration. X-ray examination revealed a large, dense circumscribed mass at the hilus in the posterior portion of the right lung, extending down behind the diaphragm. This mass had somewhat the appearance of a tumor, but the impression was that it was of an inflammatory nature, either from an old encapsulated empyema or an unresolved central pneumonia. Investigation of the genitourinary tract on this date showed no evidence of pathology.

On February 3rd the patient was much worse. He complained of pain across the chest and up into the neck. He felt weaker and was losing weight. The diastase of the urine was at the upper limit of normal.

By February 11th the jaundice had almost disappeared (serum bilirubin 5.2) but pain was still present in the upper region of the spine. The liver edge was palpable, sharp and not tender.

In order to rule out the presence of malignancy an x-ray examination of the spine was made. No definite evidence of metastasis was found but in the region of the sixth dorsal vertebra an area of rarefaction and some compression was noted. However, this finding is not at all characteristic of malignancy. Clinical examination of the spine failed to reveal any evidence of malignancy. The temperature remained normal throughout the stay in the hospital.

When this patient was admitted to the Clinic his condition was diagnosed as hypertrophic arthritis. There was no evidence of any gastrointestinal pathology either from the history or the physical examination. It is to be noted that gastrointestinal symptoms and jaundice did not occur until about January 8th, at which time he had been using cinchophen for several days. It is to be further noted that when administration of the drug was stopped, and the patient was put on treatment, the gastrointestinal symptoms and jaundice disappeared rapidly, until at the time the patient was discharged on February 15th the nausea, vomiting and jaundice had completely disappeared. I believe this evidence is sufficient to class this patient as a case of toxic hepatitis due to cinchophen.

After his discharge from the hospital the patient was not seen again and letters sent in an effort to determine his subsequent progress were returned unopened.

Case 2.— The patient, a woman 49 years of age, came to the Clinic on December 8, 1930, complaining of pain in the chest which had been present for the past ten years. The pain came in attacks and radiated up into the neck and down the right arm. It was not related to food or effort. At first the pain occurred only about once a month, but at the time the patient entered the Clinic it was occurring every few days and lasted from two to three days in the form of a dull ache. This pain had no connection with the bowels. Sick headache occurred sometimes but was not related to the pain in the chest. The attacks made the patient feel weak, but did not frighten her. The pain was accompanied by some belching of gas and some soreness in the upper right abdomen.

The patient's mother had died of diabetes associated with gangrene. One brother had died of an unknown internal disease.

The patient had had measles, mumps, and whooping cough and during the entire year, 1923, she had suffered from rheumatism which had cleared up before she entered the Clinic. Following an accident to her right hip an abscess had developed, which was drained in 1909.

The patient was a well-nourished, well-developed woman. The temperature was 98.2°, the pulse 88, blood pressure 120/80. Physical examination gave normal findings except for one enlarged node in the right axilla, and a little soreness in the right breast. No local tenderness was present in the right pectoral muscle, and all movements of the arm and shoulder were free.

The nose and throat examination revealed a deviated nasal septum and chronic tonsilitis, indicating a possible focus of infection.

The diagnosis was neuralgia of the chest and arms, chronic tonsilitis, deviated nasal setpum.

On December 22nd the patient was still complaining of distress in the right side of the chest which she said sometimes kept her awake. There was some belching of gas. X-ray examination of the gastrointestinal tract gave normal findings. The patient was started on cinchophen grs. 7.5 b.i.d., 30 tablets in all being administered.

On January 5th she still complained of gas which prevented her from eating much food. There was still some distress in the chest. She was given a prescription containing sodium salicylate, sodium bicarbonate, and sodium bromide and was advised to have her tonsils removed.

On January 8th while taking a bath the patient noticed a decidedly jaundiced condition. She had had no cinchophen for two

weeks. The clinical impression at this time was that catarrhal jaundice was present. She was given magnesium sulphate and advised to discontinue all other forms of medication.

On January 17th the patient was seen at home. She was comfortable, her only complaint, aside from increasing jaundice, being a poor appetite. She was mentally alert. She was advised to force fluids, and to take plenty of sugar. On January 26th her husband reported that the patient was much worse. She seemed delirious and would not take food. This condition had begun twenty-four hours previous to her husband's report. She was brought to the hospital in a comatose condition and was delirious at times. She was markedly jaundiced. Involuntary muscle twitchings were noted. The liver edge was not palpable and there was an increased area of cardiac dullness. Glucose and saline were forced intravenously and otherwise. Her temperature at the time of admission was 98.6°, pulse 110, blood pressure 120/75. Blood count: red cells 6,010,000, white cells 6,450, polymorphonuclears 74, small lymphocytes 24, monocytes 2. The blood urea was 27, cholesterol 176, total serum proteins 8.75, albumin 3.8, globulin 4.95.

At noon the following day the patient was catheterized and 200 c.c. of very dark colored urine obtained. She became restless and semicomatose. She was given glucose and saline intravenously, but her course continued to be progressively downward. The liver became quite atrophic as far as could be determined by percussion; there was almost no left lobe dullness, and the right lobe dullness appeared to be decreased by half. The urine which had to be obtained by catheter was scanty and contained bile 4+ and many bile stained casts. No tyrosin crystals were found in settled and centrifuged specimens. The patient died on January 30th. About thirty-six hours before death a great deal of pulmonary edema developed, but there was little or no general edema. The heart action was satisfactory at all times. The blood pressure fell gradually. Permission for an autopsy was refused.

Case 3.— The patient, a woman 31 years of age, was first seen at the Clinic on December 10, 1930. Two years previous to this time she had been operated upon for gastric ulcer, following which she had enjoyed good health until August, 1929. She then noticed a gagging sensation, with some soreness about the incision, and eructation of gas. The taking of food usually but not always aggravated the symptoms. Progressive fatigue developed, accompanied by pain in the joints, especially in the right shoulder, the right wrist, both knees and the sides of the neck. No swelling or

redness of these joints was noticed at any time, but a creaking was constantly present. The symptoms were worse during the mentrual periods. The gastric symptoms occurred about an hour after meals; there was no nausea or vomiting but appetite was decreasing and the patient was constipated.

The family history was unimportant. The patient had had no serious illnesses. Two operations had been performed — a uterine suspension in 1923 and a gastroenterostomy (ulcer) in 1928.

Physical examination revealed a well- nourished, well-developed woman 5 feet 7 inches in height, weighing 162 pounds. The temperature was 98°, pulse 72, blood pressure 132/88. The tonsils were large and appeared to be infected. Tenderness was present in the mid-epigastric region but no masses could be felt. The liver and spleen were not palpated. There were suprapubic and upper right rectus scars. On passive movement of the right wrist a creaking sensation was produced. Other joints appeared normal. The nose and throat examination disclosed hypertrophied and infected tonsils, chronic catarrhal maxillary sinusitis and ethmoiditis.

Upon dental examination, two devitalized teeth were found, and two others showed periapical absorption.

The tentative diagnosis at this time then included possible marginal ulcer, dental sepsis, infected tonsils, sinusitis, chronic ethmoiditis, mild chronic infectious arthritis.

An x-ray examination of the gastrointestinal tract showed the stomach and gall bladder to be functioning normally. A gastric analysis showed 23 per cent free acid, 36 per cent total acid. The patient was given an alkaline powder, and atropine sulphate gr. 1/100 b.i.d. and was advised to have her teeth extracted.

On December 22nd she was feeling better and was given a prescription for belladonna, hyoscyamus and bromide.

On January 7th she complained of stiffness in the neck, right shoulder, back and arms. She was again advised to have her teeth and tonsils removed and was given a prescription for cinchophen grs. 7.5 t.i.d.

On January 28th she reported that she had had her tonsils removed two weeks previous to that time. During the previous week she had been nauseated and on the day upon which she reported to the Clinic she had vomited some green fluid. On the previous day she had noted some itching of her hands and feet. She had had no cinchophen for a week, having had a total of 150 grains. On

February 2nd she had been vomiting and suffering from gas and pain in the stomach. She was very sleepy. The urine was quite dark, the vomitus was yellow in color and slimy. The patient had had several red "blisters" under her skin. Two days previously she had noted that her eyes were getting yellow.

Examination showed her to be quite jaundiced and excoriations were noticed on the legs due to scratching. There was a small spot to the inner side of the left knee and one on the palm of the left hand. There were a few black and blue marks on the right leg, above the knee, not due to trauma. The liver was tender but not palpably enlarged. There was an area of infected granulation in the upper jaw at the site of an extracted tooth.

The impression was cinchophen toxemia and infected dental granulation. The patient was given alkaline powders, a high carbohydrate diet was advised, and she was instructed to take a drahm of phosphate of soda every morning.

On February 17th the jaundice had increased, and the stools were gray. The patient was admitted to the hospital for treatment.

On examination she was found to be dehydrated and deeply jaundiced; she presented a toxic appearance, but was not undernourished. The right lobe of the liver was palpable at the costal margin. The left lobe seemed definitely smaller to percussion. No tenderness was present. The spleen was not palpable. The temperature was 98.6°, pulse 83, blood pressure 105/75. The patient was vomiting and appeared to be quite ill. She improved rapidly upon administration of glucose intravenously and a high carbohydrate and low fat diet. On February 23rd the right lobe of the liver could not be palpated and both lobes appeared smaller to percussion than before. At present the patient is almost well and will be discharged from the hospital within the next few days.

Summary

The above brief review of the history and pharmacology of cinchophen, the symptoms of toxemia resulting from the use of the drug and the method of treatment described prove definitely that the administration of this drug may be attended with grave danger, one of the three cases reported here having terminated fatally.

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