studied on the same ten subjects on different days by means of transduodenal drainage.

4. When 0.5 grams were used and transduodenal drainage was conducted over a two hour period, "B" fraction (gall bladder) bile was recovered in one case only. This is significant evidence that bile acids have practically no effect in flushing the gall bladder. When 5 cc. of oleic acid was used, "B" fraction bile was promptly obtained in each case, indicating gall bladder emptying, (cholagogue effect).

5. Cholecystographic studies made on the same ten subjects one and two hours after ingestion of 0.5 grams of bile acids and 5 cc. of oleic acid on different days closely corroborated the results obtained with duodenal drainage. Two of the ten subjects showed gall bladder emptying when bile acids were used. When oleic acid was used, nine of the ten subjects showed gall bladder emptying, manifesting itself in partial or total disappearance of the gall bladder shadow.

6. Attention is called to the fact that in five of the ten subjects the gall bladder shadow appeared enlarged either one or two hours after ingestion of 0.5 grams of bile acids, indicating distension of the viscus. The same phenomenon was observed in one case after ingestion of 5 cc. of oleic acid. The important therapeutic implication of the above in certain types of biliary tract dysfunction is pointed out.

7. The results of our observation on choleresis by means of transduodenal drainage indicate that oleic acid possesses choleraic properties, a fact proved by other investigators. The comparative choleric effects of the two drugs cannot be estimated with any degree of accuracy by the method used. There was an apparent increase in the total "A" and "C" fractions of bile recovered when oleic acid was used as compared with amounts obtained when bile acids were employed. This may have been caused in part by an admixture of succus entericus and pancreatic juice.

REFERENCES


The Influence of Phenolphthalein on the Liver*

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The quantitative determination of phenolphthalein in the urine has been reported as a test for liver and kidney function (1). In the elaboration of this test we have searched for any possible untoward consequences attributable to phenolphthalein, because of repeated assertions that phenolphthalein may be harmful to liver and kidney. These assertions are usually to be found in books of medical advice to the laity, while standard medical text books (2) do not contain such statements. This diversity of opinion prompted a study for establishing experimentally whether or not phenolphthalein may at times be harmful to the liver, as for instance cinchophen or arsphenamine have been proved to be.

Contraindications for the use of phenolphthalein are recognized in two conditions. First, phenolphthalein, as well as any other laxative, should not be used in cases of bowel pathology, particularly when there is acute abdominal pain. Second, idiosyncrasy to phenolphthalein, as manifested by skin eruptions, should exclude its use in that particular individual.

That there exists no contraindication to the use of phenolphthalein because of the possibility of kidney damage, has been shown by Fantus and Dyniewicz (3) who on urinalysis, following one thousand doses of phenolphthalein, found no albuminuria, thus disproving a previous statement by Hydrick (4). On the contrary, some observers (5) believe that phenolphthalein is the laxative of choice in albuminuric patients, and current clinical experience does not contradict this view.

In the present study we have tried to discover any contraindication to the use of phenolphthalein because of possible undesirable influence on the liver.

Reports of phenolphthalein-induced liver damage are few. The older literature contains two reports (6,
7) of jaundice, supposedly following the ingestion of three and two grains of phenolphthalein, respectively. Analysis, however, fails to substantiate these reports, as in the first case, the icterus occurred after an appendectomy and was definitely hemolytic in character; while, in the second instance, the patient developed icterus with fever on the third day after a dose of two grains of phenolphthalein. Reports of results erroneously attributed to a drug usually disappear from literature when a drug becomes well known. The reverse occurs if a drug is the evident cause of injurious influence.

Recent literature contains only one report (8) in which a liver injury from phenolphthalein was suspected; but in this case the symptoms and the necropsy findings were definitely at variance with those characteristic of hepatic injury; they were those of a widespread hemorrhagic disease; and the patient obviously died of hemiplegia due to cerebral hemorrhage.

CLINICAL METHODS AND RESULTS

Several procedures were employed in order to answer the question whether or not phenolphthalein is harmful to the liver.

I. Case histories of patients with jaundice:

Since jaundice is one of the early symptoms of liver damage, the history of icteric patients admitted to the Cook County Hospital in the past three years was carefully examined for the possibility of phenolphthalein being an etiologic factor in the development of jaundice. All together 500 cases were investigated. Special attention was directed to those with acute parenchymatous hepatitis (80) and to those with icteric cirrhosis (50).

The clinical picture of liver damage due to phenolphthalein should be similar to that of hepatitis developing as a result of a liver poison such as arsenic, cinchophen, bismuth, etc. Such damage manifests itself as a more or less severe general malaise, with increasing jaundice within 24 to 48 hours. Lassitude, anorexia, emesis, diarrhea and pruritus are frequently associated symptoms. Pain is not usually experienced except for a slight tenderness on pressure in the right upper quadrant. The liver, and at times the spleen, becomes palpable and tender to pressure. The icterus index may become very high, 100 to 150 units or more. The urine contains much bilirubin and urobilinogen and, at times, albumin. Only comparatively rarely do acholic stools occur, and then only for a short period of time. The galactose tolerance test is usually strongly positive. The cholesterol esters are low; the N.P.N. rises, and the hippuric acid excretion is markedly diminished.

In our series of cases of jaundice, we found, in two cases only, a possible connection between phenolphthalein ingestion and the appearance of jaundice, which led to an initial diagnosis of jaundice due to phenolphthalein. Both patients gave a history of dietary indiscretion, and both took moderate doses of phenolphthalein for the relief of gastro-intestinal “upset.” Because these two patients happened to take a phenolphthalein laxative rather than a saline or other cathartic, the subsequent appearance of jaundice was suspected as possibly due to the particular laxative taken. Both of these patients were given doses of five grains of phenolphthalein not only during the existence of jaundice but also later when the jaundice had disappeared. Despite these fairly large doses of phenolphthalein, neither patient showed the least signs of toxicity. It was only through a careful analysis of the history and a clinical study of these two patients, that the error in the preliminary diagnosis was demonstrated; and the cases were finally diagnosed as catarhal jaundice.

II. Phenolphthalein-tolerance test in jaundiced patients:

To a group of 120 patients, with all types of icterus, phenolphthalein was given repeatedly (two or three doses). To 50 patients, phenolphthalein was given in capsules containing 0.30 Gm. doses; while the remainder received 100 mg. of phenolphthalein in an elixir. The latter was used in order to assure better absorption of the phenolphthalein. The influence of these doses on the clinical picture and on the icteric index was noted. In some cases, other liver function tests such as the galactose tolerance test were also made. In this group there were five verified cases of arsenical hepatitis, two of bismuth hepatitis, and one of cinchophen hepatitis.

In all of these cases, most of the findings pointed to impaired liver function. They all had a high icterus index (averaging 112), positive galactose test (average excretion 3.8 grams), low cholesterol esters (averaging 37 per cent of total), low plasma proteins (average 6 mg. %), increased serum phosphatase (averaging 17 units), and increased N.P.N. (averaging 73 mg. %).

The administration of phenolphthalein to these jaundiced patients apparently in no way unfavorably influenced the course of the disease. Patients with non-malignant jaundice, who had an icterus index of 100 to 150 units when first receiving phenolphthalein, gradually improved until the icterus disappeared, as did the others who received no phenolphthalein. The galactose tolerance tests made in a number of these cases before and after phenolphthalein ingestion, failed to show any rise in the output of galactose. Indeed, in many instances the galactose tolerance improved coincidentally with the decrease in the icterus and with the general improvement.

III. Phenolphthalein-tolerance tests in non-jaundiced patients:

Similarly to the jaundiced patients, phenolphthalein was administered to 425 non-jaundiced patients suffering from various diseases, some of severe character. The cases in this group were observed for two weeks at least, following the administration of phenolphthalein; many of them for a much longer period. Although in some of these patients their disease was doubtless associated with a poorly functioning liver, in none of them did jaundice develop.

IV. Observations of liver function during prolonged phenolphthalein ingestion:

Ten patients suffering from chronic constipation in addition to other gastro-intestinal disturbance (peptic ulcer, gall bladder dysfunction, irritable bowel) were placed on 0.30 Gm. of phenolphthalein daily. This conformed most closely to their usual cathartic medication, since all of these patients had, for months or years, taken some type of laxative daily, in order to have a bowel movement. A dose of 0.30 Gm. of phenolphthalein was chosen since a dose of 0.20 Gm. which