OXYPHENISATIN INDUCED CHRONIC ACTIVE HEPATITIS – A POTENTIAL HEALTH HAZARD IN SINGAPORE

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SYNOPSIS

Three cases of oxyhenisatin induced chronic active hepatitis (CAH) are reported. The oxyphenisatin is contained within a popular Chinese laxative preparation, I-Ching Sung, widely available in Singapore without the need for a prescription. Symptoms developed after prolonged ingestion (6 months to 15 years) for chronic constipation. A drug induced mechanism was unsuspected initially by patients and their referring doctors. Two patients recovered fully following cessation of th laxative. This report aims to highlight the clinical manifestations of oxyphenisatin induced liver injury and alert the medical profession and relevant authorities of its existence.

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INTRODUCTION

The first reports of acute and chronic hepatic injury secondary to oxyphenisatin came from Reynolds in the early 1970s[1,2]. Thereafter the drug's toxic nature has been corroborated by more than 100 patients in the next 6 years. Subsequently the drug has been banned in many countries. In spite of this, sporadic cases of oxyphenisatin induced hepatitis continue to appear in patients taking from existing stocks or from sources abroad. The hepatic injury may take the form of an acute (33%) or chronic hepatitis (66%) in which case histologically chronic active hepatitis or cirrhosis is seen[3].

The 3 cases reported here presented insidiously with biopsy proven chronic active hepatitis rather than acute hepatitis.

CASE REPORT

Case I (APH)

APH, a 40 year old school teacher first presented in January 1986 with generalised lethargy, tea-coloured urine and increasing pruritus of 3 weeks duration. Four days prior to admission she became anorexic and dyspeptic. She denied fever, chills or abdominal colic. One year ago, an elective cholecystectomy was performed for dyspepsia. Of interest was the finding of a normal gallbladder with only some "mud". There was no dilatation of the common bile duct to necessitate exploration. Unfortunately no liver function tests were performed then. She had been constipated for the past 15 years. For this, she had been taking 2 to 3 tablets of I-Ching Sung, a Chinese branded laxative preparation containing 5 mgm of oxyphenisatin per tablet daily. Mogadon (Nitrazepam) was also taken on an irregular basis for insomnia. She denied a past or family history of liver disease. Clinical examination was unremarkable apart from mild jaundice. There were no stigmata of chronic liver disease. Liver and spleen were not palpable. Investigations included: Haemoglobin (Hb) 13.4 gm%; Total white (TW) count 7000/cmm [Polymorph (P) 49%, Lymphocytes (L)49%, Monocyte (M) 2%, Eosinophil (E) 0%]; Platelets (Plt) 427,000 c/mm; Erythrocyte Sedimentation Rate (ESR) 82 mm/hr; Prothrombin Time (PT) 13 sec (Control 12 sec); Partial Thromboplast in Time (PTT) 37 sec (Control 26 sec); Urea 14 mgm%, Na 132 Meq/litre, K 3.7 meq/litre, Cl 99 meq/litre, Creatinine 0.8 mgm%; Caeruloplasmin 0.45 O.D. units (Normal 0.2-0.56 O.D. unit); Antinuclear factor (ANF) +ve; Lupus erythematosus (LE) cell – ve; smooth muscle antibody (SMA) – ve; IgG 2919 mgm% (Normal 760-1600 mgm%), IgA 263 mgm% (Normal 70-380 mgm%), IgM 231 mgm% (Normal 30-160 mgm%); Hepatitis B Surface Antigen (HBsAg) – ve, Hepatitis A Antibody IgM type (Anti HAV IgM) – ve; Chest x-ray (CXR) normal; Urine bile and bile pigments +ve; Ultrasound Abdomen: No dilatation of biliary tree. Serial liver function tests (LFT) following discontinuation of the laxative preparation on 2.1.86 are shown in Table 1.

Liver biopsy (Figure 1) showed portal and periportal inflammation. Piecemeal necrosis was present. There was minimal lobular inflammation. No bridging necrosis was evident but there was increased fibrosis in the portal areas. The features were in keeping with that of a chronic active hepatitis

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Table 1: SERIAL LIVER FUNCTION TESTS OF CASE I (APH)

	30 Dec 85	2 Jan 86	10 Jan 86	17 Jan 86	4 Mar 86	27 May 86	12 Sep 86
Bil (N: 0.2-1.4 mgm%)	2.4	1.9	1.2	0.9	0.6	0.6	0.4
TP (N: 6.2-8.2 gm%)	9.5	10.7	10.6	9.8	8.9	8.4	8.0
Alb (N: 3.7-5.1 gm%)	4.0	4.0	3.9	3.9	3.8	3.9	3.9
SAP (N: 32-103 IU/litre)	228	128	126	94	72	58	56
SGPT (N: 7-36 IU/litre)	324	389	239	148	42	24	17
SGOT (N: 15-33 IU/litre)	246	301	188	103	38	28	21

Table II: SERIAL LIVER FUNCTION TESTS OF CASE II (TSG)

	11 Aug 87	18 Aug 87	3 Nov 87	
Bil	6.7	5.4	1.5	1.1
TP	6.0	6.6	6.8	7.2
Alb	2.9	2.9	3.1	3.5
SAP	164	165	115	107
SGPT	172	194	45	26
SGOT	264	287	53	34

Table III: SERIAL LIVER FUNCTION TESTS OF CASE III (LG)

	8 Aug 87	20 Nov 87	24 Nov 87	30 Nov 87	7 Dec 87	11 Dec 87	18 Dec 87
Bil	19.3	25.5	25.8	18.9	8.8	8.1	5.2
TP	6.9	6.9	7.4	7.4	6.7	6.8	6.3
Alb	3.0	2.8	3.1	2.9	2.7	2.9	2.9
SAP	86	112	122	136	119	96	95
SGPT	186	287	338	297	396	280	194
SGOT	174	422	567	583	318	191	131

FIG 1 H&E x 100

The portal tract shows a chronic inflammatory infiltrate and there is a mild degree of piecemeal necrosis.

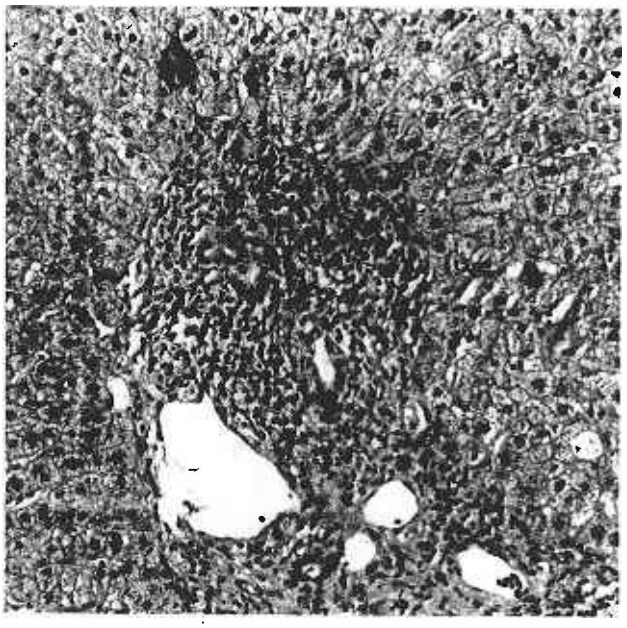


FIG 2 Reticulin x 100

Portal to portal bridging ( ) is seen and reticulin fibres form delicate extensions into the periportal areas indicating piecemeal necrosis ( ).

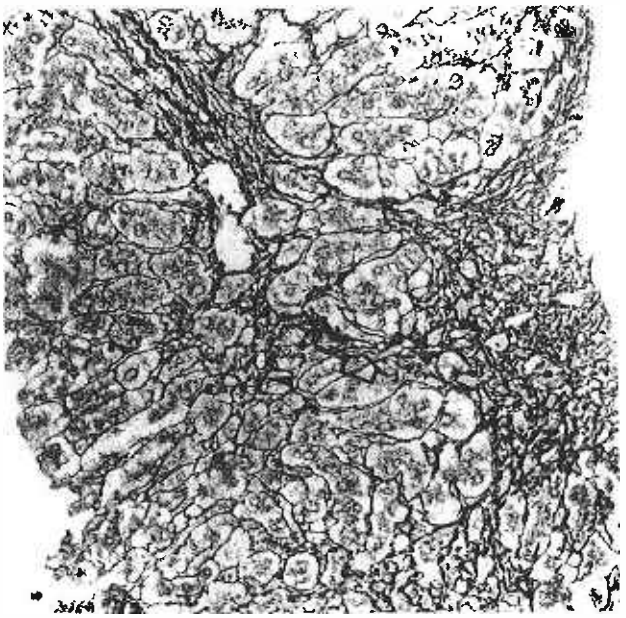
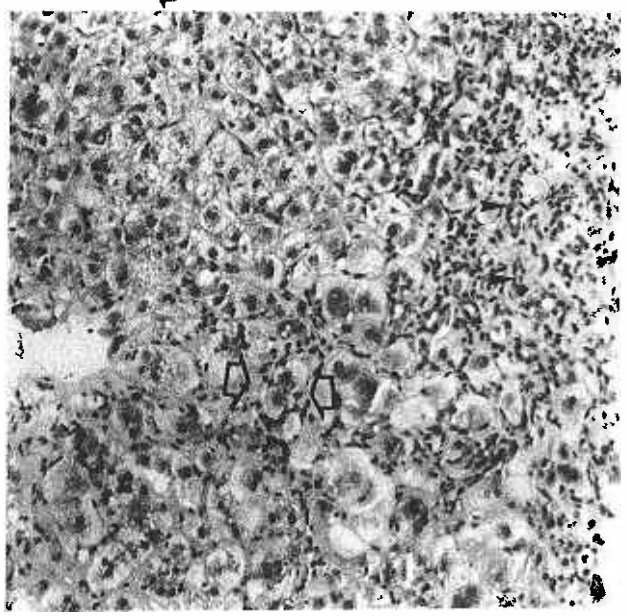


FIG 3 H&E x 100

Portal tracts show bile ductular proliferation (➤) and chronic inflammatory infiltrate. The limiting plate shows destruction and the inflammatory cells extend into the periportal areas surrounding small groups of smaller hepatocytes (⬡).



compatible with a history of oxyphenisatin ingestion. Patient initially could not accept the fact that the laxative preparation was responsible. After all, she had taken it for 15 years and could not understand why she became symptomatic in 1986 without any change in the quantity of intake. She improved clinically and biochemically following laxative withdrawal. By May 1986, her liver function tests were normal. Isogel, a bulk laxative successfully treated her constipation. She refused repeat liver biopsy.

Case II (TSG)

TSG, a 72 year old lady was admitted in August 1987 to the Surgical Department for progressively worsening constipation of 2 months duration associated with anorexia and weight loss. On examination she was thin and jaundiced but not pale. A goitre was present but there were no clinical signs of hypothyroidism. Per abdomen the liver was enlarged and firm. A pelvic mass subsequently confirmed to be a uterine fibroid was felt. Chest telangiectasia and palmar erythema were present. The provisional diagnosis by the surgeons was a gastrointestinal malignancy with metastatic spread to the liver. However barium enema and colonoscopy revealed only 3 small polyps which on removal were histologically benign. An ultrasound of the abdomen showed no liver metastases. The liver function tests showed hepatocellular dysfunction (Bil 6.7 mgm, TP 6.0 gm%, Alb 2.9 gm%, SAP 164 IU/litre, SGPT 172 IU/litre, SGOT 264 IU/litre). She denied alcoholic ingestion. Other investigations included: Hb 11.9 gm%, TW 5100/cmm (P44, L49, M4, E2, B1); T4 8.9 ugm% (N: 4.6-12 ugm%); HBsAg −ve; Urine bile and bile pigments +ve; PT/PTT normal; CXR: calcification right upper zone from old tuberculous infection. She was transferred to the Medical Department for further investigations and management. The history retaken revealed that she had been taking a Chinese laxative preparation, I-Ching Sung, about 10 tablets per week over the past 6 months. She was also an opium addict for the last 20 years. This probably contributed to her constipation. A liver biopsy (Figure 2) showed periportal hepatitis with portal to portal bridging and bile ductular proliferation.There was no evidence of cirrhosis. LE cell and ANF were negative but smooth muscle antibody (SMA) was present. Having identified the problem as that of oxyphenisatin induced chronic active hepatitis, the patient and her relatives were duly informed and warned. Her jaundice gradually disappeared while constipation was relieved with a combination of metamucil, isogel and dulcolax. Serial liver function tests following cessation of oxyphenisatin are shown in Table II.

When last seen in November 1987, the liver was just palpable and smooth muscle antibody was negative.

Case III (LG)

LG, a 79 year old lady was referred to our Department from the Medical Department of another hospital on 23.11.87. The problem was "perplexing" jaundice of 3 months duration. There was no history of alcoholic ingestion, abdominal pain, fever and chills. She denied self medication with drugs. General examination showed a markedly jaundiced lady with mild pallor. Per abdomen the liver was firm and was felt 5

Case No	Age/Sex	Date 1st Presented	Duration of Symptoms	Duration of Oxyphenisatin Ingestion	Liver Function Tests (LFT) (at presentation)						Serological Tests			HBsAg	Histology	Treatment	Normalisation of LFT
					Bil	IP	Alb	SAP	SGPT	SGOT	ANF	LE	SMA				
					mgm%	gm%		IU/lit									
I (APH)	40/F	Jan 1986	3 weeks	15 years	2.4	9.5	4.0	228	324	246	¢	-	-	-	CAH	Cessation of Drug	20 weeks
II (TSG)	72/F	Aug 1987	8 weeks	6 months	6.7	6.0	2.9	164	172	264	-	-	+	-	CAH	Cessation of Drug	12 weeks
III (LG)	79/F	Nov 1987	12 weeks	? duration	19.3	6.9	3.0	86	186	174	-	+	+	-	CAH	Cessation of Drug + Steroids	?

Key:
F – Female
Bil – Bilirubin
TP – Total Protein
Alb – Albumin
SAP – Serum Alkaline Phosphatase
SGOT – Serum Glutamic Oxaloacetic Transaminase
SGPT – Serum Glutamic Pyruvic Transaminase
LFT – Liver Function Test
ANF – Antinuclear Factor
LE – Lupus Erythematosus
SMA – Smooth Muscle Antibody
HBsAg – Hepatitis B surface Antigen
CAH – Chronic Active Hepatitis

cm below the costal margin. The spleen was not palpable. Minimal ascites was detected. There were no other stigmata of chronic liver disease. Table III shows the serial liver function tests of the patient.

Other investigations included: Hb 9.3 gm%, TW 13000/cmm (P93, L7 MO, EO,) Reticulocytes count 3.6%, ESR 25 mm/hr; Direct Coomb's Test (DCT) – ve; HBsAg – ve; Ultrasound Abdomen: Liver enlarged but with no focal lesions. Spleen slightly enlarged. No dilated bile ducts; Endoscopic retrograde cholangio-pancreatogram (ERCP): Biliary tree, gallbladder and pancreas normal; Liver biopsy (Figure 3): cholestatic hepatitis with lobular disarray, bile ductular proliferation, piecemeal necrosis and portal to portal bridging; LE cell + ve, Smooth muscle antibody + ve, Mitochondrial Antibody – ve, caeruloplasmin 0.38 O.D. units (N: 0.2-0.56).

In view of the clinical and histological picture highly suggestive of severe autoimmune (Lupoid) chronic active hepatitis, she was started on prednisolone 30 mgm/day on 5.12.87. However even before steriods were started, the liver became smaller and the LFT had started to improve. Her LE cells and smooth muscle antibody became negative 2½ weeks after admission. The patient's family was questioned again regarding the history of drug ingestion which the patient had earlier denied. Two days before discharge on 17.12.87 they brought a bottle of I-Ching Sung tablets. The bottle was found among the patient's belongings. Patient refused to say how long, how much and how often she had been taking the medication apart from the fact that it was meant for constipation. In the hospital, agarol was given daily as early as 4 days after admission with good result. This pointer if noticed earlier might have led to an earlier diagnosis but was overlooked. The patient and relatives were warned of the dangers of I-Ching Sung tablets. However she failed to return for follow up despite repeated calls to do so. When last contacted in January 1987, we were told she was too ill and reluctant to come to review. The possibility of continued ingestion of I-Ching Sung tablets could not be discounted. Table IV summarises the clinical features, laboratory and immunological findings and management of the 3 cases.

DISCUSSION

Constipation is a preoccupation with many people particularly the old. In Singapore the situation is probably no different. The wide array of Western and traditional laxative preparations in the market is testimony to its frequency. The intake of laxative can become so accepted as a part of normal healthy living that many fail to recognise that these drugs may be potentially harmful[3].

Oxyphenisatin, C24H1905N [synonyms include Isaphen, Isapeninum, diacetyl diphenolisatin, acetophenolisatin, diacetophenyl oxindol, bisitin, isacen, 3,3 bis (p-hydroxphenyl) 2-indilinone diacetate] a peristaltic stimulant was popularly used in laxative preparations in the early 1960s. Following reports of its potential for inducing liver injury, particularly chronic active hepatitis, many such preparation (e.g. Agarolet, Dialose P, Prulet, Prulose Complex, Bekunis) have been withdrawn or banned from the Western and Australian markets4. However one such preparation from China is available in Singapore. It is sold over the counter in many Chinese medicinal shops under the trade name "I-Ching Sung". Literally translated, "I-Ching Sung" in Chinese means "total release/relaxation at one go". With such a catchy name, the brand's local appeal is assured. Furthermore each tablet which contains 5 mgm of oxyphenisatin is sold at a give-away price of about 3 Singapore cents.

All three patients reported had idiopathic constipation. Case I and II's histories of constipation and laxative ingestion were readily elicitable. Case III was problematic. Diagnosis came after her relatives searched her belongings. Constipation was not admitted initially but agarol was served to the patient daily in hospital. In dealing with chronic active hepatitis of uncertain aetiology, a history of constipation elicitable in the history or observed in the ward, may be an important clue to the diagnosis of oxyphenisatin ingestion. That all 3 patients are female is no coincidence as this is supported by the findings of others [2,3,4,5,6]. Presumably this is related to greater use of laxatives in this sex. The duration of oxyphenisatin ingestion ranged from 6 months (Case II) to 15 years (Case I). This is in keeping with the observation of Maddry[7] who noted a minimum duration of ingestion of 6 months in patients who develop chronic active hepatitis.

The mechanism of liver injury from oxyphenisatin is unknown and controversial. Reynolds[1,2] favoured a hypersensitivity mechanism based on the more rapid appearance of jaundice following rechallenge. However, Goldstein supported Dujovne's[8] finding from tissue culture and pahrmacokinetic experiments that the mechanism is a dose dependent direct toxic effect. The latter also suggested that laxative induced chronic liver disease is not entirely secondary to oxyphenisatin but also to another ingredient, dioctyl sodium sulphosuccinate (DSS) present in some laxative preparations. However, analysis of I-Ching Sung tablets consumed by all 3 patients showed no other ingredient besides oxyphenisatin.

The clinical features in our patients with oxyphenisatin induced chronic active hepatitis were basically that of insidious development of symptoms. Jaundice ranged from mild (Bil 2.4 mgm% (Case I] to severely cholestatic [Bil 19.3 ngm% (Case III)]. The degree of transaminitis in our patients ranged between 150 to 350 IU/litre fairly typical of chronic active hepatitis. Eosinophilia was not present and thus not helpful in suggesting a drug induced cause. The absence of eosinophilia has been noted before[9]. Confusion is further created by the appearance of immunological epiphenomena (Positive antinuclear factor, smooth muscle antibody, LE cell)[2,10] and hyperglobulinemia mimicking autoimmune/lupoid chronic active hepatitis. The close similarity makes differentiation from autoimmune/lupoid chronic active hepatitis difficult. In fact, Cooksley[11] believes that many patients in the past may have been diagnosed and managed erroneously for autoimmune/lupoid chronic active hepatitis without fully exploring the possibility that oxyphenisatin is the culprit.

Prognosis for recovery is good following cessation of oxyphenisatin. All 3 cases lost their immunological markers at follow-up. Steroids were administered in Case III but so far no controlled trials have shown benefit from steriods[12]. Case I and II had total resolution of symptoms and biochemistry on follow up. Case III though forewarned at discharge may be deteriorating from continued ingestion. Progression of chronic disease after the drug has been stopped, appears to be rare[5]. However, continued ingestion may lead to cirrhosis and death from liver failure[3].

Of the 3 patients, 2 (Case II and III) has been extensively investigated prior to referral to our department. The clinical points in the history viz. constipation and laxative ingestion were either not sufficiently pursued, or altogether ignored, resulting in the diagnosis being missed. This suggests that many doctors are not aware of the association between chronic ingestion of oxyphenisatin and liver injury. Oxyphenisatin is the most frequently implicated drug in the causation of chronic active hepatitis[12]. Being retailed so cheaply and freely available over the counter, it is surprising that the occurrence of oxyphenisatin induced chronic active hepatitis is not more common. So far only 2 laxative preparations available in Singapore contain oxyphenisatin, namely I-Ching Sung and Prutab(Unichem). Another possible source that needs to be explored is the health food shop. Kotha[13]

in 1980 reported a case of chronic active hepatitis secondary to the ingestion of oxyphenisatin contained in a laxative preparation Silklax. This preparation was sold in a health food shop at a time when it was believed that oxyphenisatin was unavailable in Britian.

We have reported these cases of oxyphenisatin induced chronic active hepatitis to the Drug Administration Division, Ministry of Health, Singapore in January 1988. This report meanwhile aims to draw the attention of the medical profession to oxyphenisatin as a health hazard.

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