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Scenario 4: Choice of hormone replacement therapy (HRT)

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Introduction

During the menopause a reduction in the levels of oestrogen and progesterone takes place. This results in women experiencing, among others, vasomotor symptoms (such as hot flushes and night sweats) and vaginal symptoms (dryness, itching and discomfort). In most women, hot flushes are transient and usually resolve within four to five years. However, vaginal symptoms generally persist and can worsen with aging [1]. Hormone replacement therapy (HRT) is therefore used to try to alleviate these symptoms. The benefits of short-term HRT outweigh the risks in the majority of women, especially in those aged under 60 years. Experience in treating women over 65 years with HRT is limited [2].

Owing to the reduction in oestrogen levels during the menopause, an increase in bone loss is seen. However, HRT is generally not recommended as first-line therapy for the prophylaxis or treatment of postmenopausal osteoporosis. It should only be used where other therapies are contraindicated, not tolerated, or there is a lack of response.

HRT is designed to restore the premenopausal physiological state. This is in contrast to oral contraceptive pills, which contain much higher concentrations of oestrogen and progestogen, required to suppress ovulation. HRT consists of a small dose of oestrogen, given either alone or in combination with a progestogen in women with an intact uterus. The progestogens are given either cyclically or continuously.

Reduction in bone density is an important complication and cause of morbidity in chronic liver disease. This can lead to osteoporosis and osteomalacia with resulting bone fractures, pain, deformity and immobility. The problem is greatest in cholestatic liver diseases such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). In postmenopausal women with PBC the rate of bone loss can occur at twice

the normal rate (2% vs 1% per year) [3]. Vertebral fracture is the most commonly described fracture in patients with chronic liver disease [4].

Osteoporosis is also common in those on long-term corticosteroid therapy (for example patients with autoimmune hepatitis or coexisting inflammatory bowel disease). Patients with chronic liver disease may also have other risk factors for osteoporosis related to their disease state. These include vitamin D deficiency, excessive alcohol consumption, poor diet, physical inactivity and low body mass index. Oestrogen deficiency in the postmenopausal stage further increases the risk.

HRT has been shown to be effective in reducing bone loss and fractures in postmenopausal women. It inhibits bone resorption and stimulates new bone formation [5]. When HRT is given in the first five to ten years of menopause the long-term risk of osteoporotic fractures is halved [5].

The risks and benefits of HRT should be carefully assessed on an individual basis. This is particularly important in women with predisposing risk factors, such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity or prolonged best-rest [2], because HRT increases the risk of venous thromboembolism and stroke. HRT has also been observed to increase the risk of gallbladder disease, breast cancer and endometrial cancer. It is recommended that the minimum effective dose should be used for the shortest period of time, with treatment being reviewed at least once a year [2].

In women with an intact uterus a progestogen should be added to reduce the risk of endometrial hyperplasia and possible transformation to cancer. However, the addition of a progestogen should be weighed against the increased risk of breast cancer associated with its use.

Summary

The use of HRT is generally cautioned in liver disease because of concern over its potential to provoke or worsen cholestasis. This is based on early experience with oral contraceptive pills that contained higher doses of the less degradable synthetic oestrogen ethinylestradiol. However, several studies have demonstrated the safety and efficacy of HRT in patients with chronic liver disease, in particular those with PBC and viral hepatitis. HRT may be particularly beneficial in patients with PBC owing to the high prevalence of osteoporosis in this population. Consensus guidelines for the management of osteoporosis in patients with chronic liver disease recommend transdermal HRT (containing

oestradiol 50 μg/day plus progestogen in women with an intact uterus) in combination with oral calcium and vitamin D supplementation, as first-line therapy.

The pharmacokinetics of oestrogen and progestogen can be significantly altered in patients with liver disease. Oestrogens and progestogens are highly lipophilic, therefore oral absorption may be reduced in patients with cholestasis. Both oestrogen and progestogen undergo extensive first-pass metabolism in the liver. However, newer HRT preparations usually contain either a readily degradable oestradiol or conjugated equine oestrogens. Amongst the progestogens, norethisterone derivatives have more of an effect on liver metabolism than do the progesterone derivatives [6].

In patients with portal hypertension impaired blood flow to the liver may decrease the first-pass metabolism of oral oestrogen and progestogen, with a resulting increase in bioavailability. In addition, their binding and distribution may be affected in patients with low albumin, as they are highly protein bound. However, the clinical significance of these changes is unknown. It would therefore be prudent to monitor the patient closely for efficacy and safety during treatment.

The metabolites of both oestrogen and progestogen are excreted into the bile. Oestrogen metabolites undergo extensive enterohepatic circulation before being eliminated in the urine. Progestogens do not undergo enterohepatic circulation and their metabolites are excreted mainly in faeces and urine.

In patients with cholestasis, biliary excretion may be impaired, reducing the overall drug exposure, which could lead to decreased efficacy. However, such effect has not been reported in the clinical studies involving oral HRT.

The transdermal or subcutaneous routes are more favourable as they avoid first-pass metabolism. However, subcutaneous implants may result in prolonged endometrial stimulation, even after discontinuation. Topical therapy may be used to provide symptomatic relief of vaginal symptoms.

A small increase in the risk of gallbladder disease has been associated with the use of HRT. Studies have shown that preparations containing oestrogen alone are associated with a greater risk than combination oestrogen/progestogen therapy. The formulation used is important, with transdermal preparations considered safer. Studies have also suggested that women who are already jaundiced are most at risk of increased cholestasis with HRT.

Before starting HRT patients should be assessed individually considering their risk of osteoporosis, the current status of their liver disease, and any other coexisting medical risks. They should also be assessed for any history, including family history, of jaundice. The risks and potential benefits of treatment should be carefully explained.

Liver enzymes and serum bilirubin should be measured before treatment is commenced to indicate the degree of cholestasis. These parameters should then be closely monitored, with treatment being stopped if a significant increase is seen. The optimum duration of treatment has yet to be defined, but it is recommended that the minimum effective dose should be used for the shortest period.

Unless otherwise stated, all pharmacokinetic data originate from standard reference sources [28–32] and apply to adults only.

Pharmacokinetics

See Table 12.1 for a summary of the pharmacokinetics of HRT in adults.

Absorption

Orally administered oestrogens are completely absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within one-half to five hours. Bioavailability is low due to extensive first-pass metabolism in the small intestinal mucosa and liver. Many of the commercially available oral preparations of HRT contain formulations of oestrogens that release slowly over several hours.

Orally administered progestogens are also completely absorbed from the gastrointestinal tract, with peak serum levels occurring within one to five hours. The bioavailability of progestogens varies greatly.

Oestrogens and progestogens can also be administered by subcutaneous implants or transdermally, thereby avoiding first-pass metabolism. These routes cause a slower and more prolonged increase in plasma concentrations of hormones compared to oral administration. HRT is usually given transdermally or orally, although topical gels for vaginal use are also available.

Tibolone is rapidly and extensively absorbed. The extent of presystemic metabolism, and hence bioavailability, is not known.

Raloxifene is rapidly absorbed following oral administration. It then undergoes extensive first-pass metabolism (presystemic glucuronidation).

Distribution

Oestrogens and progestogens are widely distributed in the body and are found in higher concentrations in the sex hormone target organs. Once absorbed, oestrogens and progestogens are transported in the blood to the liver, mainly bound to plasma proteins or sex hormone-binding globulin (oestrogens only). A small proportion (1–5%) is transported as free steroid (unbound).

Data on the distribution of tibolone are limited. It is transported in the blood to the liver 96% bound to plasma proteins, most likely albumin.

Raloxifene is distributed extensively throughout the body, with the volume of distribution being dose dependent. It is highly protein bound (98–99%) to plasma proteins, including albumin.

Metabolism

Orally administered oestrogens undergo extensive first-pass metabolism in the small intestinal mucosa and liver by a hydroxysteroid dehydrogenase. These metabolites are converted to glucuronide and sulphate conjugates. Unlike ethinylestradiol, oestradiol is readily oxidised to oestrone and oestriol.

Progestogen metabolism is not as widely documented, but it also undergoes first-pass metabolism. The major route of liver metabolism is via hydroxylation, with subsequent conjugation and elimination. The clinical significance of many progestogen metabolites is unknown.

Tibolone is rapidly broken down into three active metabolites, two having oestrogen-like activity, the third having progestagenic and androgen-like activity. *In-vitro* studies have suggested that tibolone may undergo tissue-selective local metabolism. The relevance of this is, however, unknown [7].

Elimination

After metabolism, conjugates of oestrogens and progestogens are excreted into the bile. Following subsequent biliary secretion into the intestine, the oestrogen metabolites undergo hydrolysis, followed by reabsorption. This is known as enterohepatic circulation. This means that there is a constant circulating reservoir for the formation of the active oestrogen metabolites. Oestrogen metabolites and conjugates are eliminated in the urine.

Table12.1 Pharmacokinetics of HRT in adults

Drug	*Bio-availability*	T_{max} *(hrs)*	*Lipophilicity*	*Protein binding %*	*Half-life (hrs)*
Drospirenone (oral)	76–85%	1	–	97	36–42
Estradiol (oral)	Low	0.5–5	High	97–99	2–16
Estradiol (transdermal)	–	36–42	–	97–99	2–16
Medroxyprogesterone acetate (oral)	Low	2–6	High	94	30
Norethisterone acetate (oral)	64%	0.5–2	High	90–95	6–11
Norethisterone acetate (transdermal)	–	37–48	–	90–95	6–15
Raloxifene	2%	28	–	>95	28
Tibolone	Unknown	1.5–4	High	96	–

% excreted unchanged in urine	*% Biliary excreted*	*Metabolism*	*Active metabolites*
Mainly excreted as metabolites	Excreted as metabolites in faeces	Extensive metabolism	The two major metabolites are pharmacologically inactive
Mainly excreted as metabolites	40% Undergoes enterohepatic circulation	Extensive first-pass metabolism in gut and liver Reduction, hydroxylation and conjugation to form both glucuronide and sulfate conjugates	Oesterone Oestriol
Mainly excreted as metabolites	40% Undergoes enterohepatic circulation	No first-pass effect Reduction, hydroxylation and conjugation to form both glucuronide and sulfate conjugates	Oesterone Oestriol
<5%	–	Extensively metabolized Undergoes hydroxylation, de-esterification, transesterification, demethylation, conjugation, reduction	Unknown
Low Excreted mainly as metabolites	Excreted as metabolites in faeces	First-pass metabolism Reduction then conjugated with glucuronide or sulfate	Norethisterone 5α-dihydronorethisterone Tetrahydronorethisterone
Low. Mainly excreted as metabolites in urine	Excreted as metabolites in faeces	Reduction then conjugated with glucuronide or sulfate	Norethisterone 5α-dihydronorethisterone Tetrahydronorethisterone
< 0.2% Less than 6% excreted as conjugates	>90%. Undergoes enterohepatic circulation Excreted as metabolites in faeces	Extensive first-pass metabolism Glucuronide conjugates formed	Unknown
Excreted as metabolites (40%)	Excreted as metabolites in faeces (60%)	Extensive metabolism in liver and intestine	3β-hydroxytibolone 3α-hydroxytibolone Tibolone-4-ene

Progestogens do not undergo enterohepatic circulation. Metabolites are excreted in the faeces and urine. Only a small proportion of a dose of progestogen is excreted unchanged in the urine.

Tibolone does not undergo enterohepatic circulation. Excretion occurs mainly via the faecal route, with urinary excretion accounting for the remainder.

Raloxifene undergoes enterohepatic circulation, allowing the maintenance of plasma levels and giving it a longer half-life. The majority of a dose of raloxifene and its metabolites are excreted via biliary excretion, with elimination in the faeces. Only a small proportion is excreted via the urine [8].

Some relevant adverse effects

Hepatotoxicity

Because the dose of oestrogens and progestogens used in HRT products is low, the majority of women experience no adverse effects on liver function. Occasionally hepatic changes such as cholestatic jaundice, vascular complications and enlargement of haemangiomas have occurred. See the Clinical studies and Case reports section below for further details.

Biliary effects

An increased risk of gallbladder disease has been associated with the use of HRT [9].

Gastrointestinal effects

Abdominal pain and bloating have been associated with the use of HRT.

Some relevant drug interactions

Concomitant use of substances known to induce cytochrome P450 enzymes, in particular CYP3A4, may increase the metabolism of oestrogens and progestogens, leading to reduced effect and changes in the uterine bleeding profile. Conversely, drugs that inhibit these enzymes may reduce metabolism, leading to a higher exposure. The clinical significance of this is, however, unknown.

In clinical practice drug interactions are relatively uncommon in women using HRT, owing to the low doses of oestrogen and progestogen used.

There is no evidence that tibolone causes enzyme induction. In theory, substances that induce cytochrome P450 may affect the metabolism of tibolone and lead to reduced activity. However, no interactions between tibolone and other medicines have been reported in clinical practice [7].

No clinically important interactions have been reported when raloxifene is co-administered with several groups of drugs, including analgesics [8].

Clinical studies and case reports

Women without liver disease

Two small studies have examined the effect of HRT on liver function tests in healthy women. The women had regular assessment of their liver function tests during therapy. Hepatotoxicity and cholestasis were not observed [10, 11].

Observational data have suggested that HRT users may have a better profile of liver function tests. One randomised placebo-controlled study involving 50 women with type 2 diabetes demonstrated that HRT containing oestradiol 1 mg and norethisterone 0.5 mg significantly improved serum concentrations of liver enzymes. The authors hypothesised that this might be due to HRT causing a reduction in liver fat content. However, further work in this area to understand the significance and mechanisms by which this occurs was recommended [12].

HRT has also been shown to cause favourable changes in serum lipid levels in normal postmenopausal women [13]. This effect could be particularly beneficial in women with cholestatic liver disease who may have elevated serum cholesterol.

Women with cholestatic liver disease

Many of the studies looking at the use of HRT in liver disease involve women with PBC, owing to the high prevalence of osteoporosis in this population (approximately 30%) [14]. In a small retrospective study of postmenopausal women with PBC, 16 received HRT. This was shown to cause a significant increase in bone mineral density in the lumbar spine compared to the untreated group at one-year follow-up. No

worsening of cholestasis was observed in the HRT group [15]. However, the dose, form and duration of HRT therapy used in this study were not consistent. Another similar study involving ten women with PBC (nine with osteoporosis and one with osteopenia) who received HRT for two years also found that HRT was safe and effective [16].

The findings of these studies were confirmed by a longer retrospective study involving 46 women with PBC. HRT significantly lowered the rate of bone loss compared to age-matched untreated women. This study had a much longer follow-up period (4.8 ± 0.4 years), but also demonstrated that HRT is safe and effective in PBC [17]. However, as with the previous studies, the HRT preparations used were not standardised.

The effect of ethinylestradiol 50 μg daily on liver function tests was examined in five women with PBC. These patients had been previously exposed to various HRT preparations (oestrogen or an oestrogen–progestogen combination). Three of the women, who had normal or near normal serum bilirubin before treatment, tolerated HRT well. However, the remaining two, who were profoundly jaundiced (with serum bilirubins of 193 μmol/L and 365 μmol/L, respectively) before treatment, experienced a further increase in serum bilirubin levels two to three months after starting treatment. A decrease in bilirubin levels occurred in both patients upon withdrawal of ethinyloestradiol [18].

The findings of this study suggest that women who are already jaundiced at the initiation of HRT are most at risk of increased bilirubin levels and cholestasis. In view of this it would seem sensible that, as well as assessing bilirubin levels prior to treatment, women who want to take HRT should also be assessed for any history (including family history) of jaundice. This will include specific defects in bilirubin excretion, such as intrahepatic cholestasis of pregnancy or familial conjugated hyperbilirubinaemia, which may worsen cholestasis.

The safety and efficacy of transdermal HRT was examined in a one-year controlled trial involving 42 postmenopausal women with PBC [19]. They were treated with calcium and vitamin D either alone or combined with HRT. A total of 21 women received HRT (13 received combination oestradiol and norethisterone, with the remaining eight receiving oestradiol alone). The follow-up period was one year. Those receiving HRT plus calcium and vitamin D showed improved lumbar spine bone mineral density compared to the group receiving calcium and vitamin D alone. No significant change in liver function tests was observed. In particular, worsening of cholestasis was not seen despite nine of the 21 patients receiving HRT having raised serum bilirubin

levels (mean bilirubin 29.6 ± 4.9 μmol/L) prior to the start of treatment and one being clinically jaundiced (65 μmol/L). The effect of HRT on this particular patient's bilirubin level was unfortunately not discussed further in this study [19].

A similar study involving 18 postmenopausal women with PBC looked at the safety and efficacy of transdermal HRT over a two-year period. The women were randomised to receive both calcium and alfacalcidol, either alone or in combination with HRT (oestradiol and medroxyprogesterone). A significant increase in bone mineral density in the lumbar spine and femoral neck was seen in the group receiving HRT [14]. One patient was withdrawn from the study because of a significant rise in AST (three times above baseline) and ALT (five times above baseline) levels. No change in ALP or bilirubin was observed. Upon withdrawal of treatment AST and ALT returned to baseline levels within three months. The authors concluded that, in the absence of other factors, oestrogen therapy was the likely cause of this [14].

Women with viral hepatitis

The safety of transdermal HRT (oestradiol 50 μg/day, norethisterone 250 μg/day for 14 days per 28-day cycle) was investigated in 81 postmenopausal women with chronic hepatitis B and/or C. The liver enzymes of these women remained unaffected after five years of treatment. In those with signs of hepatomegaly or steatosis of the liver, HRT actually seemed to slow the progression toward liver fibrosis [20]. A similar result was also seen in a retrospective study of women with hepatitis C receiving HRT. This study suggested that HRT appeared to be associated with a protective effect against the progression of fibrosis [21]. This has also been demonstrated in an animal study which showed that endogenous and exogenous oestrogens have a protective effect on liver fibrosis [22]. A positive effect of oestrogens on liver cirrhosis, potentially linked to the antioxidant properties of oestradiol, has also been suggested [23].

Risk of gallbladder disease

An increased risk of gallbladder disease has been associated with the use of HRT. This is believed to be due to oestrogens and progestogens causing an increase in levels of biliary cholesterol while reducing the relative level of bile acids. This leads to an increase of cholesterol saturation in bile, predisposing to gallstone formation. Gallbladder contractility may also be affected [9].

Several studies have tried to quantify the risk of gallbladder disease in women receiving HRT. The Heart and Oestrogen/Progestin Replacement Study found that gallbladder disease occurred in 3% of patients who received HRT, compared to 2.2% of those who received placebo [9]. Two Women's Health Initiative trials showed a greater risk of gallbladder disease or surgery with oestrogen alone than with oestrogen and progestogen preparations. In women who were receiving oestrogen alone, there were 78 events per 10 000 person-years, compared to 55 events per 10 000 person-years in women receiving combined preparations [9].

The formulation of HRT used may also affect the risk of gallbladder disease. One small study involving 17 patients compared transdermal oestradiol (100 μg daily) to oral oestradiol (2 mg daily). It found that, unlike with oral therapy, transdermal oestradiol did not induce lithogenic bile or increase the risk of gallstone formation [24]. Oral oestrogen therapy causes a more pronounced increase in oesterone levels than does transdermal administration. This increase correlates with an increase in the cholesterol saturation index, which can lead to gallstone formation [9, 24, 25]. This finding is supported by other studies showing that transdermal oestrogen appears to have less of an effect on liver function than oral administration [24, 25]. This is thought to be because transdermal oestrogens more closely mimic physiological oestrogen/oestradiol ratios. Therefore, transdermal therapy may be advantageous in patients with cholestatic liver disease, particularly PBC, in which gallstones are common.

Raloxifene

Raloxifene undergoes extensive first-pass metabolism to glucuronide conjugates. It is then eliminated by biliary excretion. The pharmacokinetics of raloxifene have been studied in patients with mild hepatic impairment (Child–Pugh class A) and concentrations and were found to be approximately 2.5 times higher than in controls, correlating with the patient's bilirubin concentration [8].

Recommendations on the use of HRT in liver disease

Williams *et al.* [26] have recommended that HRT should be considered '**…**in all women with chronic liver disease who are postmenopausal, have primary or secondary amenorrhoea, or have had oophorectomy'. Transdermal therapy is preferred. Serum bilirubin and liver enzymes

should be measured before treatment is initiated to indicate the degree of cholestasis. These tests should then be repeated one month after treatment is started. If the serum GGT and ALP have not increased by more than 100%, and the serum bilirubin has remained normal, then treatment can be continued. Liver function tests should then be monitored every six months. On the other hand, if the serum GGT and ALP have increased by more than 100%, or if serum bilirubin has risen, liver function tests should be checked every month for at least three months. Treatment should be stopped if a significant increase is seen [26].

Consensus guidelines on the management of osteoporosis associated with chronic liver disease recommend oral calcium and vitamin D supplementation plus transdermal HRT as first-line therapy for women with established osteoporosis. Transdermal oestradiol should be used at a dose of 50 μg/day (equivalent to 2 mg daily of oral oestradiol). This should be given in combination with a progestogen in women with an intact uterus [4]. Oral bisphosphonates should be avoided in cirrhotic patients who may have portal hypertension and oesophageal varices because of their potential to precipitate a variceal bleed [4, 27].

The risks and benefits of HRT should be assessed for each patient by taking into consideration individual risk factors and the severity of their liver disease. These should be discussed with the patient before the initiation of therapy. Liver function tests should be monitored before treatment is begun, and then during treatment as appropriate. The optimum duration of therapy has yet to be defined in liver patients. The minimum effective dose should be used for the shortest period. The decision to continue treatment must be made on an individual basis, in view of the risks associated with use of HRT.

CASE STUDIES

Patient 1 – Mild hepatitis without cirrhosis

The synthetic and metabolic capacity of this patient's liver is unlikely to be affected by the isolated rise in ALT, and drug handling is unlikely to be altered. It is important to ensure that the patient has no signs of cirrhosis, as many diseases that present with this clinical picture can become cirrhotic despite near normal laboratory tests.

- In the treatment of menopausal symptoms the benefits of short-term HRT may outweigh the risks, especially in this patient, who is under 60 years of age.

- Apart from protection against osteoporosis, HRT is also associated with favourable changes in serum lipid levels in postmenopausal women. This may be helpful in this patient, who has fatty liver disease.
- HRT has also been associated with a protective effect against the progression of fibrosis. However, this has yet to be confirmed in a large randomised controlled trial.
- The best choice for this patient would be HRT via the transdermal route, as this avoids first-pass metabolism. Although the synthetic and metabolic capacity of the liver is unlikely to be affected, oral therapy should be avoided.
- Ethinylestradiol is not recommended as it is less degradable. Therefore, an oestradiol-containing preparation should be used.
- A combination product containing oestrogen and progestogen should be used if the patient has an intact uterus.
- The lowest effective dose for shortest period of time should be used.
- Liver function tests should be measured before treatment is started. These should then be monitored closely during treatment. Treatment should be stopped if a significant change occurs.

Patient 2 – Cholestasis

The synthetic and metabolic capacity of this patient's liver is unlikely to be affected by cholestasis. However, consideration needs to be given to protein binding (patient has hyperbilirubinaemia); excretion of the drug or metabolites in bile (patient has cholestasis); and the lipophilicity of the drug (some lipophilic drugs require bile salts for absorption, and these would be reduced in cholestasis).

- Loss of bone density is an important complication and particularly common in cholestatic liver diseases such as PSC. Therefore, HRT would be beneficial in this patient.
- Although the synthetic and metabolic capacity of the liver is unlikely to be affected, oral therapy should be avoided. Oestrogens and progestogens are highly lipophilic, therefore absorption may be reduced.
- Oestrogens undergo enterohepatic circulation. As this patient is cholestatic, biliary excretion may be impaired. This may reduce the overall exposure to the drug, which could lead to decreased efficacy. However, this was not reported as a problem in the clinical studies involving oral HRT that have been carried out in similar patient populations.
- Ethinylestradiol is not recommended as it is less degradable. Therefore, an oestradiol-containing preparation should be used.
- A combination product containing oestrogen and progestogen should be used if the patient has an intact uterus.

- As this patient has cholestasis they may be at a higher risk of HRT causing a further increase in bilirubin levels and worsening cholestasis. Liver function tests should be measured before treatment is started, and be monitored closely during treatment. Treatment should be stopped if a significant change occurs.
- The patient should be checked for any skin sensitivity before using the transdermal patch. Any skin reaction may worsen pruritus already suffered by the patient.
- The lowest effective dose for the shortest period of time should be used.

Patient 3 – Compensated cirrhosis

Despite cirrhosis, this patient is maintaining good hepatocyte function (normal albumin and bilirubin, mildly raised INR) and the metabolic and excretory capacity of the liver should not be significantly reduced. The patient has portal hypertension, so blood flow to the liver will be impaired, which will reduce the first-pass metabolism of highly extracted drugs (extraction ratio >0.7). This will result in greater bioavailability of oral doses of these drugs. It is important to note that the patient could rapidly deteriorate into a state of decompensation where liver function would be markedly affected.

Other things to consider are the raised INR and low platelet count, the risk of encephalopathy if the liver function decompensates, and the risk of hepatorenal syndrome.

- Oral therapy should be avoided as oestrogens and progestogens undergo extensive first-pass metabolism. Therefore, exposure to the drug would be increased, with a resulting increased risk of hepatotoxicity.
- The best choice for this patient would be HRT via the transdermal route, as this avoids first-pass metabolism.
- Ethinylestradiol is not recommended as it is less degradable. Therefore, an oestradiol-containing preparation should be used.
- A combination product containing oestrogen and progestogen should be used if the patient has an intact uterus.
- The lowest effective dose for the shortest period of time should be used.
- Liver function tests should be measured before treatment is started. These should then be monitored closely during treatment. Treatment should be stopped if a significant change occurs.
- The patient should be checked for skin sensitivity before using the transdermal patch. Any skin reaction may worsen pruritus already suffered by the patient.

Patient 4 – Decompensated cirrhosis

HRT (oral and transdermal) should not be initiated or continued in patients with decompensated cirrhosis. The hepatocyte damage is irreversible and can only worsen over time. The significant reduction in metabolic capacity and reduction in hepatic of blood flow will lead to drug accumulation, with consequent increased risk of hepatotoxicity. There is also the potential to worsen the cholestatic picture in this patient, who is already profoundly jaundiced.

Patient 5 – Acute liver failure

There is no place for HRT in a 16-year-old girl. HRT is also otherwise contraindicated in acute liver failure. The rapid hepatocyte damage has led to poor synthetic function and a significant reduction in the ability of the liver to metabolise the drug. This will only result in drug accumulation and hence added hepatotoxicity in acute liver failure.

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