Tamsulosin and Hepatic Failure: Case Study, Review of Literature and Summary of Hepatic effects of Common Urological Medications

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Abstract

ObjectivesReview of hepatic failure as a side effect of alpha blockers and common urologic drugs in generalPatients and MethodsCase study of 65 year old female patient developing deranged LFTs following tamsulosin used as medical expulsive therapy. Review of literature regarding alpha blockers and hepatic failure. Summary of hepatic effects of medications in common urological useResultsSingle reported case of hepatitis induced by tamsulosin. Cohort study shows no increased risk of hepatic failure with tamsulosin. Hepatic failure an established feature of certain urological medications – co-amoxiclav, antiandrogens, diethylstilbestrol, duloxetine, pentosanConclusionMost commonly used drugs in urology, including tamsulosin, significantly affect hepatic function only rarely. Awareness is required in those that more frequently affect the liver

CASE STUDY

A 65 year old lady presented with a 2 hour history of left ureteric colic with microscopic haematuria on urinalysis preceded a week earlier by a single episode of painless frank haematuria. Past medical history included appendicectomy and hysterectomy and no regular medication prior to this episode; in particular this patient had no history of liver failure and was on no hepatotoxic medications. The patient had previously taken acetaminophen with no ill effects indeed had no previous drug adverse events. Family history included a mother with systemic lupus erythematosus. Physical examination revealed only left flank tenderness. On admission we prescribed morphine, diclofenac and cyclizine for symptom control.

CTKUB (kidney, ureter bladder views with no contrast) demonstrated a 5mm calculus in the distal left ureter with moderate hydroureteronephrosis above but also 2 incidental left renal lesions which on a subsequent contrast CT scan were indicated to be renal tumours. No liver pathology was seen on either scan. Blood tests demonstrated no significant abnormalities of renal/liver function although there was a borderline gamma-glutamyl transferase (GGT) of 77.

The patient settled clinically on analgesia (including paracetamol of which the patient received a total of 8g over 4 days) and was informed of the 2 diagnoses and need for left nephrectomy then discharged on a course of tamsulosin as medical expulsive therapy. The patient's pain settled completely and while paracetamol and diclofenac were prescribed on discharge the patient took only up to 1g of acetaminophen per day for one week only.

During preoperative work-up for left radical nephrectomy 2 weeks later the patient was found to have significantly deranged liver function tests (LFTs) Alanine transferase 161, Alkaline Phosphatase 405, GGT 654. The patient had no new symptoms in regard to this. Since the patient was on no other regular medications this was ascribed to tamsulosin and the medication discontinued. Following discontinuation liver function improved with all but GGT normalising within 3 months. The patient underwent a radical left nephrectomy 5 weeks later at which time the stone was removed ureteroscopically.

LITERATURE REVIEW: TAMSULOSIN AND HEPATIC IMPAIRMENT

Tamsulosin is a superselective 1-antagonist licensed for use in males for benign prostatic hypertrophy (BPH). Following multiple papers[1, 2] demonstrating improved passage of ureteric calculi and reduced colic symptoms with -blockers it is used (off license in the UK) for medical expulsive therapy. Tamsulosin is extensively metabolised in the liver by CYP3A4 and CYP2D6 but is not commonly associated

with deranged LFTs or liver failure.

Known side effects of tamsulosin include orthostatic hypotension, ejaculation disorders, dizziness, rhinitis and allergic reactions. Liver impairment/deranged LFTs are not listed as side effects in the most recent British National Formulary (BNF)[4] or internet drug index[3]. The BNF recommends avoidance in severe hepatic impairment (table 1). The internet drug index further clarifies this in that while in moderate hepatic impairment levels of unbound (active) tamsulosin are not significantly altered and intrinsic clearance changed only by 32%, this has not been studied in severe hepatic impairment[3,5].

Figure 1

Table 1: Summary of Recommendations for Urological Drugs in Hepatic Impairment

Medication	Mild Impairment	Moderate Impairment	Severe Impairment
α-blockers	Fine	Fine	Avoid
Co-amoxiclav	Monitor	Monitor	Monitor
Ciprofloxacin	Fine	Fine	Fine
Trimethoprim	Fine	Fine	Fine
Nitrofurantoin	Caution	Caution	Caution
Cephalosporin	Fine	Fine	Fine
Anti Androgen	Monitor	Caution/Monitor	Caution/Monitor
LHRH Agonist	Fine	Fine	Fine
Diethyltilbestrol	Avoid	Avoid	Avoid
Zoledronic Acid	Fine	Fine	Caution
Anticholinergic	Fine	Reduce	Avoid
Duloxetine	Avoid	Avoid	Avoid
5α-Reductase Inhibitors	Fine	Fine	Avoid (Dutasteride)
Pentosan	Caution/Monitor	Caution/Monitor	Caution/Monitor
Amitriptyline	Fine	Fine	Avoid
DMSO	Monitor	Monitor	Monitor

Database search (MEDLINE, Pubmed, Cochrane, EMBASE, CINAHL, HMIC, NHS Evidence, TRIP database) for tamsulosin or alpha blockers cross-referenced with liver failure and variants thereof yields only a single French article reporting a possible association between tamsulosin and hepatitis[6]. To the author's knowledge therefore this is the first reported hepatic impairment secondary to tamsulosin in English language literature.

Conversely a single cohort analysis demonstrated no increased risk of liver injury in a population of 9666 men on -blockers compared to a similar population not exposed to them[7]. The same paper reports no significant difference using case control analyses. A single paper demonstrates a possible protective effect of the selective 1-antagonist Prazosin against hepatotoxicity caused by paracetamol in mice as assessed by serum transaminases and glutathione[8]. Tamsulosin itself demonstrates neither a protective nor damaging effect. In conclusion, aside from a single source, -blockers are not detrimental to hepatic function and may even be protective.

REVIEW: HEPATIC IMPAIRMENT IN UROLOGY MEDICATIONS

Given the importance of renal physiology in urology a great deal of attention is given to nephrotoxins in urology patients but a number of medications commonly used in urology can exert a hepatotoxic effect of which we must be aware.

ANTIBIOTICS

Co-amoxiclav: a combination of amoxicillin and clavulanic acid used frequently in urinary tract infections (UTIs) suitable for complicated infections particularly -lactamase producing E coli and Klebsiella. Co-amoxiclav has the well established side effect of cholestatic jaundice which is dose-dependent and usually self-limiting. More likely in men and in over 65s caution and LFT monitoring is required if a patient already has liver impairment[4]. Co-amoxiclav additionally may cause acute hepatitis[9] with hepatocellular changes on biopsy[3, 10]. Mortality related to co-amoxiclav hepatic damage is circa 1 in 4 million prescriptions worldwide.

Ciprofloxacin: the most prominent of the quinolones used extensively for gram negative and positive UTIs, prostatitis, epididymo-orchitis with prolonged courses in chronic prostatitis. LFT derangement occurs in up to 1.3%[3]; both hepatitis and cholestasis are rare complications of quinolones and fatal cases have been reported[11] not necessarily dose dependent[12]. Hepatic dysfunction is not a contraindication in the BNF.

Trimethoprim: antibacterial used in uncomplicated UTIs. Transient rises in transaminases and bilirubin occur but are of unclear significance. Cholestatic jaundice is rare. Again hepatic dysfunction is not a contraindication.

Nitrofurantoin: antibacterial used in uncomplicated UTIs and long term prophylaxis. Nitrofurantoin is reported as causing acute hepatitis, chronic hepatitis, cholestasis and hepatic necrosis with fatalities reported. It is to be used with caution in hepatic dysfunction[4] with monitoring of hepatic function as onset of chronic hepatitis may be slow.

Cephalosporines: transient hepatitis and cholestatic pictures have been reported but are rare and hepatic impairment not a specific contraindication.

Anti Androgens: Inhibitors of the androgen receptor bicalutamide, flutamide and cyproterone used in prostate cancer alone or as adjuncts. Cholestatic jaundice is a well described side effect with periodic liver function tests suggested particularly in prolonged therapy. Chlolestasis is dose dependent and cumulative in moderate and severe hepatic impairment leading to fulminant hepatic failure[13]. A hepatitic picture can occur[14] as can fatality[15]. LFT derangement occurs in up to 11% of patients on anti-androgen/LHRH analogue combinations and ~1% patients on Casodex in clinical trials require drug withdraw due to liver failure[3]. Pre and in treatment LFT monitoring is particularly emphasised with cyproterone acetate. Manufacturers recommend caution regarding anti-androgen commencement in moderate to severe hepatic impairment however no specific dose adjustment is recommended.

LHRH Analogues: agonists of LHRH receptor use in prostate cancer used as monotherapy are not linked to liver failure and hepatic impairment is not an impediment to their use. In a trial of Zoladex in female patients <1% had a rise in transaminases with no causation established[3].

Diethylstilbestrol (DES): oestrogen used in hormone resistant prostate cancer. DES shares the side effect profile of other oestrogens such as the combined contraceptive pill which includes hepatic dysfunction, cholestasis and hepatic adenoma and carcinoma. Avoidance is recommended in any pre-existing hepatic dysfunction including disorders of hepatic excretion due to impaired oestrogen excretion[4].

Anticholinergics: used in detrusor instability and urge incontinence LFT derangement is not reported as a significant side effect. Manufacturers recommend caution in using anticholinergics in established hepatic impairment with precise advice dependant on the specific drug but typically altering the dose at moderate impairment and avoidance if severe. This is based on significant increases in drug half life (e.g. doubling in solifenacin) in moderate hepatic failure.

Zoledronic Acid: intravenous bisphosphonate used in metastatic prostate cancer. No associated hepatic failure, caution recommended in severe hepatic impairment due to limited studies.

Duloxetine: a noradrenaline/serotonin reuptake inhibitor licensed for use in female stress incontinence. Duloxetine has a rare side effect of severe, even fatal[15], hepatotoxicity characterised by markedly raised transaminases in a hepatocellular or mixed pattern. In trials significantly raised transaminases occur in up to 1.1% patients[3]. LFT derangement may be cholestatic. Due to these side effects and a massively reduced (15%) plasma clearance in moderate hepatic failure, pre-existing hepatic impairment contraindicates duloxetine.

5α-Reductase Inhibitors: used in BPH for prostatic volume reduction hepatic impairment is not a significant side effect and major trials do not report deranged LFTs. Due to these medications being metabolised extensively in the liver levels would presumably be raised in hepatic failure therefore they are proscribed in severe hepatic impairment however there is no specific data underlying this[3].

Phophodiesterase 5 Inhibitors: used in erectile dysfunction. Hepatic dysfunction is not a significant side effect however manufacturers recommend lower doses at severe hepatic impairment.

Penotosan Polysulphate Sodium: oral heparin-like agent used in interstitial cystitis. Pentosan is principally metabolised by desulphation in the liver with deranged LFTs occurring in 1.2% of patients (11.8% in phase 2 trial with higher than recommended dose)[3]. The effect is usually transient but may progress therefore caution is recommended in patients with pre-existing hepatic insufficiency and LFTs may be monitored routinely.

Amitriptyline: Tricyclic antidepressant (TCA) used for symptomatic control of interstitial cystitis. TCAs are also primarily metabolised in the liver and hepatitis, hepatic failure and jaundice are rare side effects. Due to this and exacerbated sedative effect severe hepatic dysfunction contraindicates amitriptyline.

Dimethyl Sulphoxide (DMSO): Intravesical instillation therapy for interstitial cystitis. Hepatic failure is not a listed side effect or contraindication but the BNF recommends a precautionary 6-monthly check of hepatic function.

In summary while most drugs in common use in urology, including tamsulosin, significantly affect hepatic function only rarely awareness is required in those – anti androgens, co-amoxiclav, DES, duloxetine and pentosan which more frequently affect the liver and which require pre therapy

testing or surveillance.

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